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Evaluation and Development of Practical Routes to an Enantiomerically Pure C_2 Symmetrical Diamine Building Block

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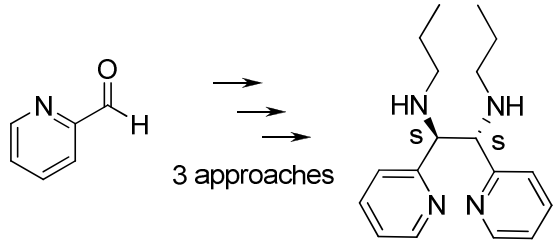
SYNOPSIS

Evaluation and Development of Practical Routes to an Enantiomerically Pure C_2 Symmetrical Diamine Building Block



ABSTRACT: Several routes to an enantiomerically pure C_2 symmetrical diamine were evaluated and modified to scalable methods. A Zn/Me_3SiCl mediated reductive coupling of an imine was found to be superior to the other methods investigated allowing us to safely prepare the enantiomerically pure diamine also on a large scale. One key step in this method was a highly

efficient resolution of a stereoisomeric mixture of the diamine through salt formation with (-)-dibenzoyl-L-tartaric acid. The enantiomerically pure C_2 symmetrical diamine obtained was further used as a key building block for the synthesis of potent Kv1.5 channel blockers.

INTRODUCTION: Enantiomerically pure C_2 symmetrical diamines are attractive targets for use as chiral ligands in asymmetric synthesis.[1] In addition to the importance of these in this field, we also identified such types of symmetrical diamines as building blocks for the synthesis of potent Kv1.5 ion channel blockers. To be able to run a full toxicology program we needed several hundreds of grams of the symmetrical diamine (*S,S*)-**1** which further could be substituted on the secondary amines to give the desired API AZD-**2502** (Figure 1). We considered to utilize the commercially available diamine (*S,S*)-**2** as starting material. However, since this diamine was very expensive and only a few suppliers were available we sought a scalable route to obtain the diamine (*S,S*)-**1** or (*S,S*)-**2**. This would secure material needed to select a candidate for treatment of arrhythmia.

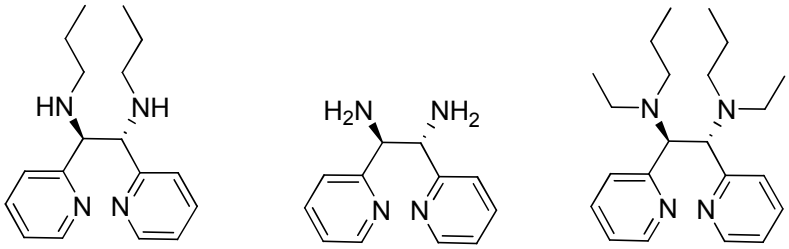


Figure 1. Building blocks for the synthesis of Kv1.5 ion channel blockers such as AZD-**2502**.

RESULTS AND DISCUSSION

A literature survey of methods to synthesize diamines of type **1** and **2** revealed that several methods were available (Figure 2).[2] To prepare screening compounds for the lead optimization

program, an approach via an epoxide was used (approach **A**, Figure 2).[3] Although this approach was suitable for the preparation of a range of diverse screening compounds within a short period of time, it suffered from low selectivity in the coupling step to the epoxide and the necessity to separate enantiomers through chromatography at a later stage. Also, we were concerned with the use of hexaethylphosphorous triamide in the coupling step since this reagent is transformed into hexaethylphosphoric triamide (HEPA) which is an analogue to the well known carcinogenic HMPA. Furthermore, the reagent was expensive and not easily accessible. In the evaluation of routes to the diamine (*S,S*)-**1** we initially chose five approaches (approach **B**-**F**) depicted in Figure 2 which we believed would have the greatest chance to be scale-up friendly.

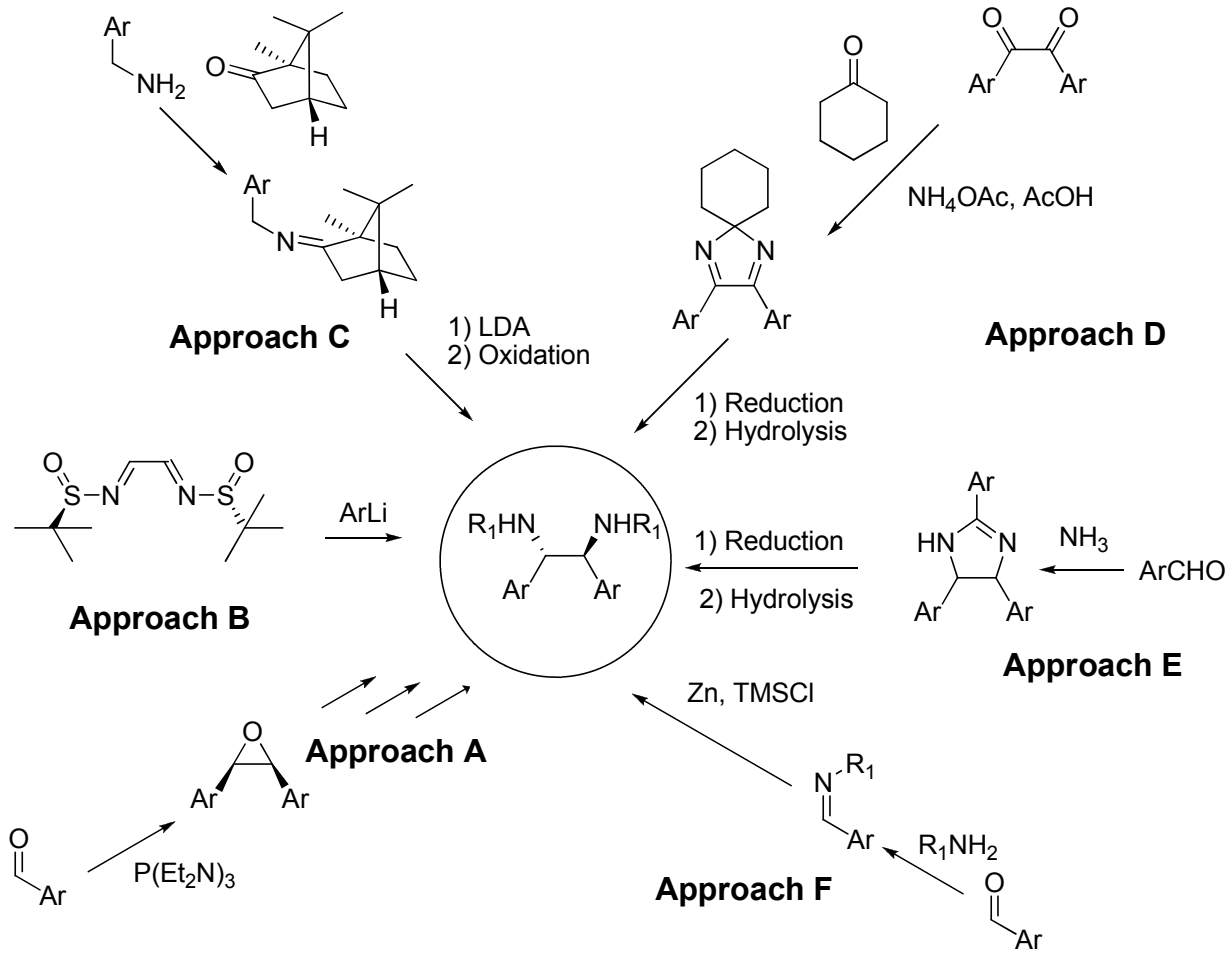


Figure 2. Various approaches available to obtain the C_2 symmetrical diamines **1** or **2**.

APPROACH B-C.

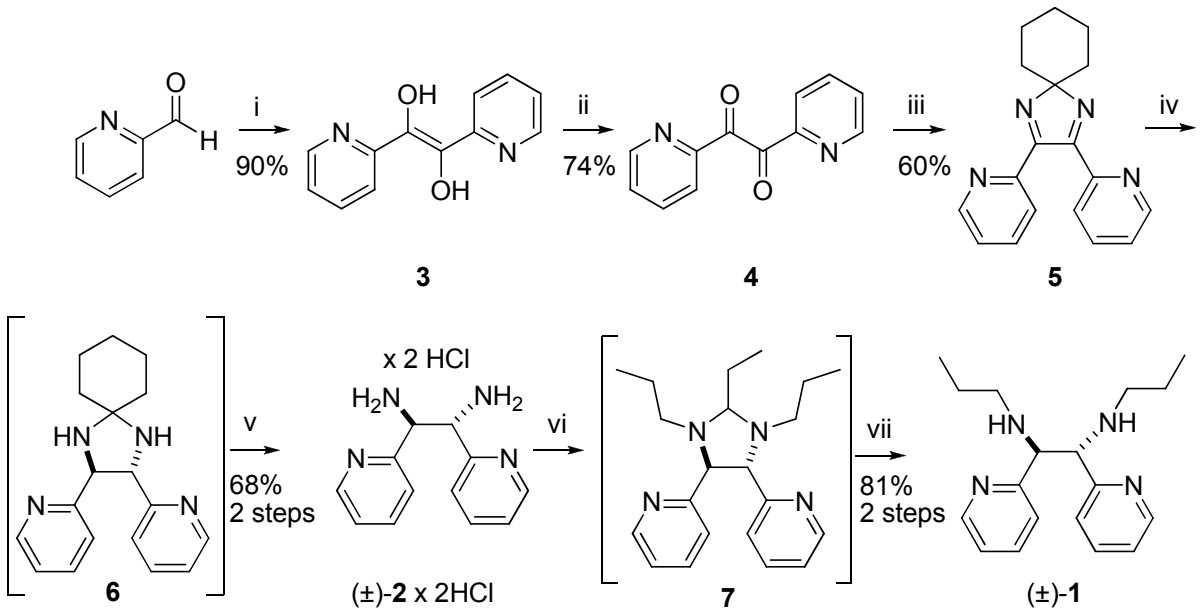
Among the six methods depicted in Figure 2, we first believed that the method described by Deng et al.[2e] (Approach B) would be suitable for our purpose because it would furnish the enantiomerically pure diamine (*S,S*)-**1** without having to resolve enantiomeric mixtures. However, despite several attempts using various conditions with Grignard and lithium carbanions, we were not able to obtain a satisfactory yield and diastereoselectivity for this transformation. We decided to abandon this approach and instead turn to another asymmetric method described by Yaozhong et al. (Approach C).2[b] In this approach a chiral auxiliary (*i.e* camphor) is condensed with 2-aminomethylpyridine. The resulting imine undergoes an oxidative coupling mediated by various oxidants to give diastereomerically enriched diimines in good selectivity, which after hydrolysis furnish the diamine (*S,S*)-**2**. However, very soon we realized that the method did not give the result that we expected. The reaction was performed several times using various oxidants such as Fe(III), 1,2-dibromoethane and Br_2 but we were not able to reproduce the result obtained by Yaozhong et al. Incomplete conversion of starting material and a very low diastereoselectivity were obtained and it was clear that this method was not suitable for further scale-up work. We realized that a non-asymmetric method followed by resolution of enantiomers had to be considered to obtain the desired diamine (*S,S*)-**1** or (*S,S*)-**2**.

APPROACH D.

In a paper by Corey et al.,2[f] a non-asymmetric method is described where an aromatic diketone is condensed with cyclohexanone and NH_4OAc to give the corresponding diimine (Approach D). The authors were then able to reduce the diimine to the corresponding trans-

diamine. After hydrolysis, the corresponding racemic primary diamines could be liberated and then resolved into pure enantiomers through salt formation with tartaric acid. We decided to evaluate this route further but starting from 2-pyridinecarboxaldehyde. Using this approach we were able to secure 1.2 kg of the dihydrochloride salt of the racemic diamine (±)-**2** x 2HCl after some development work according to Scheme 1.

Scheme 1. Approach D[a].

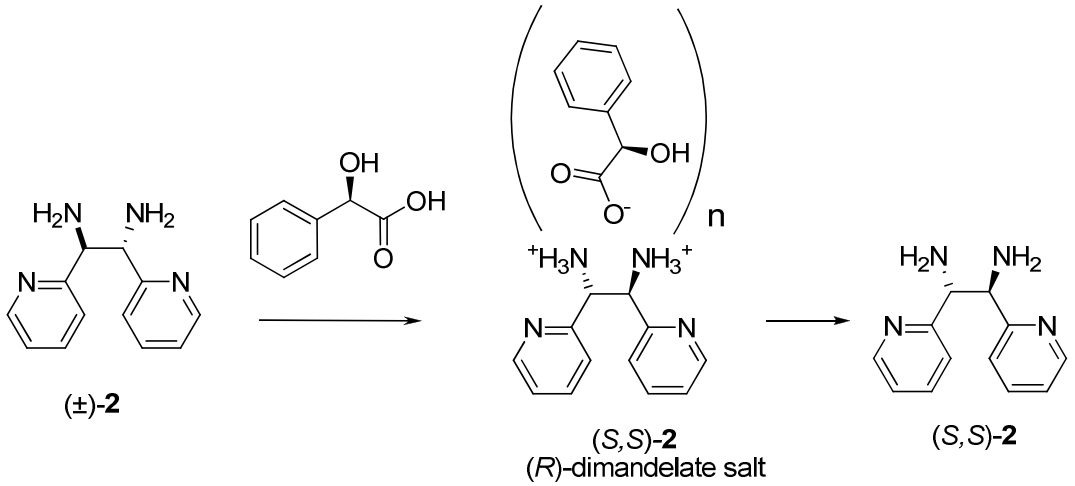


[a] Reaction conditions: (i) KCN, H_2O/pyridine, reflux; (ii) I_2, NaOAc, EtOH; (iii) cyclohexanone, NH_4OAc, HOAc, 40 ^oC; (iv) Mg, MeOH, 40 ^oC; (v) HCl/2-propanol; (vi) propionaldehyde, $NaBH(OAc)_3$; (vii) 3M HCl, 1-propanethiol.

The diketone **4**, although commercially available, seemed to be quite labile and we were not able to purchase pure material in sufficient amount from any supplier. Therefore we prepared this freshly via the enediol **3**[4] obtained from the commercially available 2-pyridinecarboxaldehyde. The oxidation of **3** to **4** was initially carried out according to a procedure involving NaBrO generated from Br_2.[5] However, we found that the procedure could be simplified by carrying out the oxidation with I_2 in equally high yield, and thus avoiding the

handling of large amounts of bromine. The diketone **4** was then condensed with cyclohexanone and ammonia to give the diimine **5** that was ready for a stereoselective reduction. We found that magnesium (0) as reducing agent in MeOH gave the most consistent results and we could abandon other inconvenient reducing methods such as Li(0) and Na(0) reductions in liquid NH_3 which had to be carried out at very low temperatures (-78 ^{o}C) to avoid reduction of the pyridine rings. The obtained trans diastereomer **6** was then treated with HCl which hydrolyzed the *N,N*-ketal leaving the dihydrochloride salt of the pure diamine (±)-**2** x 2HCl as an insoluble crystalline solid in 70% yield. At this stage we wanted to resolve the enantiomers prior to further manipulations. We wanted to avoid the use of chromatography and therefore we screened a selection of chiral acids and we were finally able to resolve the racemate through salt formation with (*R*)-mandelic acid providing the dimandelate salt of the diamine (*S,S*)-**2** in 96% ee (Scheme 2). However, the resolution was challenging and control over the stoichiometry of acid/amine was essential to obtain high enantiomeric purity of the product. This was due to a switch in relative solubilities of the diastereomeric salts when having a 1:1 salt (n = 1) compared with a 1:2 salt (n = 2, Scheme 2). Moreover, it was found that a too high loading of the mandelic acid resulted in an almost racemic product. When analyzing this salt by ^{1}H NMR it was found that the ratio of acid/amine exceeded 2 (n > 2, Scheme 2) meaning that probably a third molecule of mandelic acid was part of the salt through hydrogen bonding making the crystallization even more troublesome.

Scheme 2. Resolution of (±)-**2** through salt formation with (*R*)-mandelic acid, n = 2.



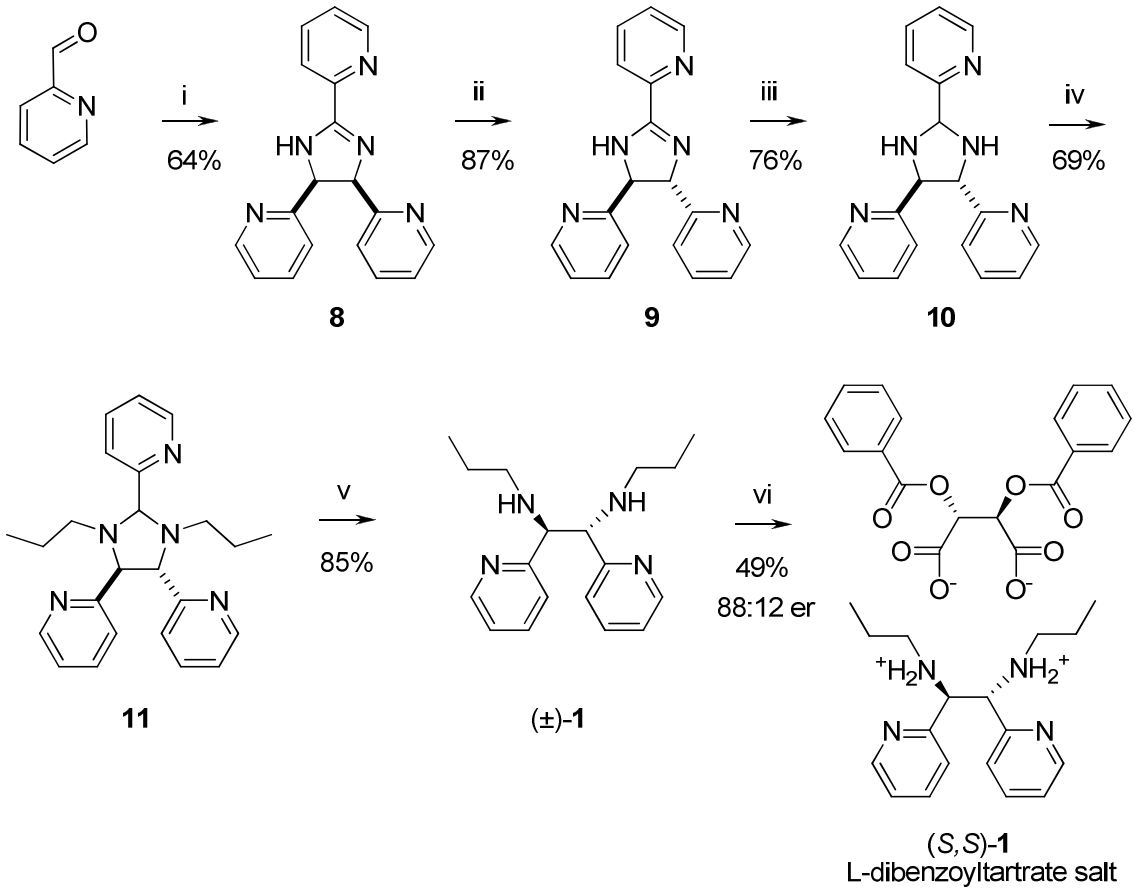
On a small scale (20 g), the 1:2 mandelate salt of (*S,S*)-**2** isolated after one crystallization from EtOAc/CH_2Cl_2 was reductively alkylated followed by a hydrolysis to give (*S,S*)-**1** following the procedure described for the racemate in Scheme 1. We were able to determine the enantiomeric purity of (*S,S*)-**1** by chiral HPLC (97:3 er). The scale up (800 g) of the resolution of (±)-**2** through salt formation with (*R*)-mandelic acid failed and a very low enantiomeric purity was obtained of the diamine (*S,S*)-**2** for reasons as described above. We were at that time under pressure to deliver material for the toxicology studies and to save time we decided to move on with the racemic material and separate the enantiomers at a later stage through chromatography.[6] Using the approach as described in Scheme 1, we were able to prepare 394 g of the diamine (±)-**1**. After separation of the enantiomers via chiral chromatography followed by the final synthetic step we were able to successfully deliver the desired API in time for the initial toxicology studies. However, we were a bit concerned of many of the steps for further scale-up. In addition to the long linear sequence to (±)-**1** (total overall yield = 22%), the reduction of **5** to **6** with Mg was highly exothermic and time-consuming on a larger scale. Moreover, the resolution of the racemate (±)-**2** was not as straightforward as we first expected and a lot of efforts would

probably be needed to develop a working process. Therefore, as a back-up we searched for a shorter route where such issues could be avoided.

APPROACH E.

It is known that 2-pyridinecarboxaldehyde in the presence of an aqueous solution of ammonia undergoes condensation furnishing the cis-dihydroimidazole **8** (Scheme 3).[7] By treatment with a strong base, **8** epimerizes to give the trans-dihydroimidazole **9**.[7] In our hands, this procedure was easily reproduced and gave **9** in 87% yield. By some modifications of the original procedure we were able to develop a scale-up friendly method that gave consistent results. A potential route to the enantiomerically pure diamine (*S,S*)-**2** from **9** could then be via separation of the enantiomeric mixture of **9** mediated by acetylmandelic acid as has been shown for an analogue.[8] However, it would require harsh conditions to hydrolyze the mandelic amide (HBr in AcOH) and this operation was foreseen to be impractical on a large scale. Instead our plan was to reduce **9** to give the corresponding imidazolidine **10** followed by resolution of the enantiomers at a later stage. The reduction devised by Corey and Kühnle[9] using aluminum amalgam in wet THF was rejected for environmental reasons. We reasoned that acylated **9** may be easier to reduce but after having tried several conditions[10] on Boc-protected **9** we turned back on finding alternatives for reducing **9**. An initial futile attempt using Na/Naphthalene was followed by a much more successful combination of zinc and acetic acid that after some optimization cleanly gave the desired aminal **10**. We found that the imidazolidine **10** was stable under alkaline conditions but rapidly hydrolyzed under acidic conditions (pH 1-2). Our plan was to utilize the 2-pyridinecarboxaldehyde unit as a protective aminal group to avoid excessive alkylation in the following reductive alkylation step.

Scheme 3. Approach E[a] **.**

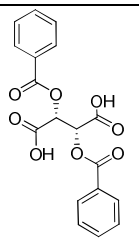
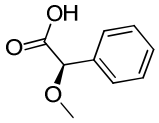
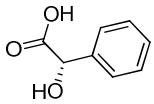
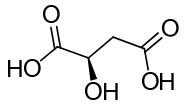
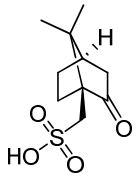
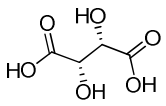


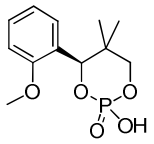
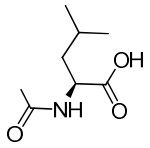
[a] Reaction conditions: (i) 26% NH_3 (aq.), THF; (ii) K-amylate (0.02 equiv.), THF; (iii) Zn, HOAc, 2-methyl-THF; (iv) propionaldehyde , DIPEA, sodium triacetoxyborohydride, THF; (v) HCl, 1-propanethiol (6 equiv.); (vi) (-)-dibenzoyl-L-tartaric acid (50 mol%), EtOAc/heptane.

Treatment of **10** with propionaldehyde in the presence of sodium triacetoxyborohydride gave the alkylated product **11** in 69% yield. In an attempt to optimize the route for further scale-up we investigated if the reduction of **9** and alkylation of **10** could be telescoped. Thus we wanted to use the Me-THF solution of **10** after the extractive work-up directly in the next step. However, we found that the reductive alkylation was best performed using EtOAc as solvent and it was also an advantage to use reasonably dry solvents. When run with the crude wet Me-THF solution of **10**, incomplete conversions were obtained and the reaction mixtures in some cases turned into a unfavorable two-phase mixture. Thus we decided to concentrate the Me-THF

solution of **10** prior to the reductive alkylation step and use EtOAc as solvent instead. What remained to be done to reach the diamine (±)-**1** was the hydrolytic removal of the 2-pyridinecarboxaldehyde moiety. This was easily accomplished by direct treatment of the acidic aqueous layer, after the work-up of **11**, with propanethiol to trap the aldehyde formed after hydrolysis. In order to resolve the enantiomers we screened for chiral acids that would furnish a salt with suitable properties (Table 1).

Table 1. Salt screen performed in order to find a suitable acid for the resolution of (±)-**1**.[a]

Entry	Resolving acid[b]	Type of salt	Yield	Er **1**[c]
1		1:1	49%	97:3
2		--[d]	--	--
3		--[d]	--	--
4		1:1	20%	0%
5		--[d]	--	--
6		1:1	~ 10%	0%

7		--[d]	--	--
8		1:2	25%	92:8

[a] Salt formation in EtOAc or EtOAc/heptane mixtures on a small scale (0.3 mmol). [b] 50-70 mol% of the resolving acid was used. [c] Determined using chiral HPLC. [d] No solid material obtained.

Fortunately we found that both dibenzoyltartrate (1:1 salt, entry 1) and *N*-acetyl leucine (1:2 salt, entry 8) formed a salt with desired properties, the former salt yielding a much better result. On a 5 g scale, we obtained the dibenzoyltartrate salt of (*S*,*S*)-**1** in 49% yield with a slightly lower enantiomeric ratio (88:12 er) of the free amine as compared with the small scale experiment (97:3 er, entry 1, Table 1). One more recrystallization from EtOAc gave the stereoisomerically pure (*S*,*S*)-**1** L-dibenzoyltartrate salt.[11]

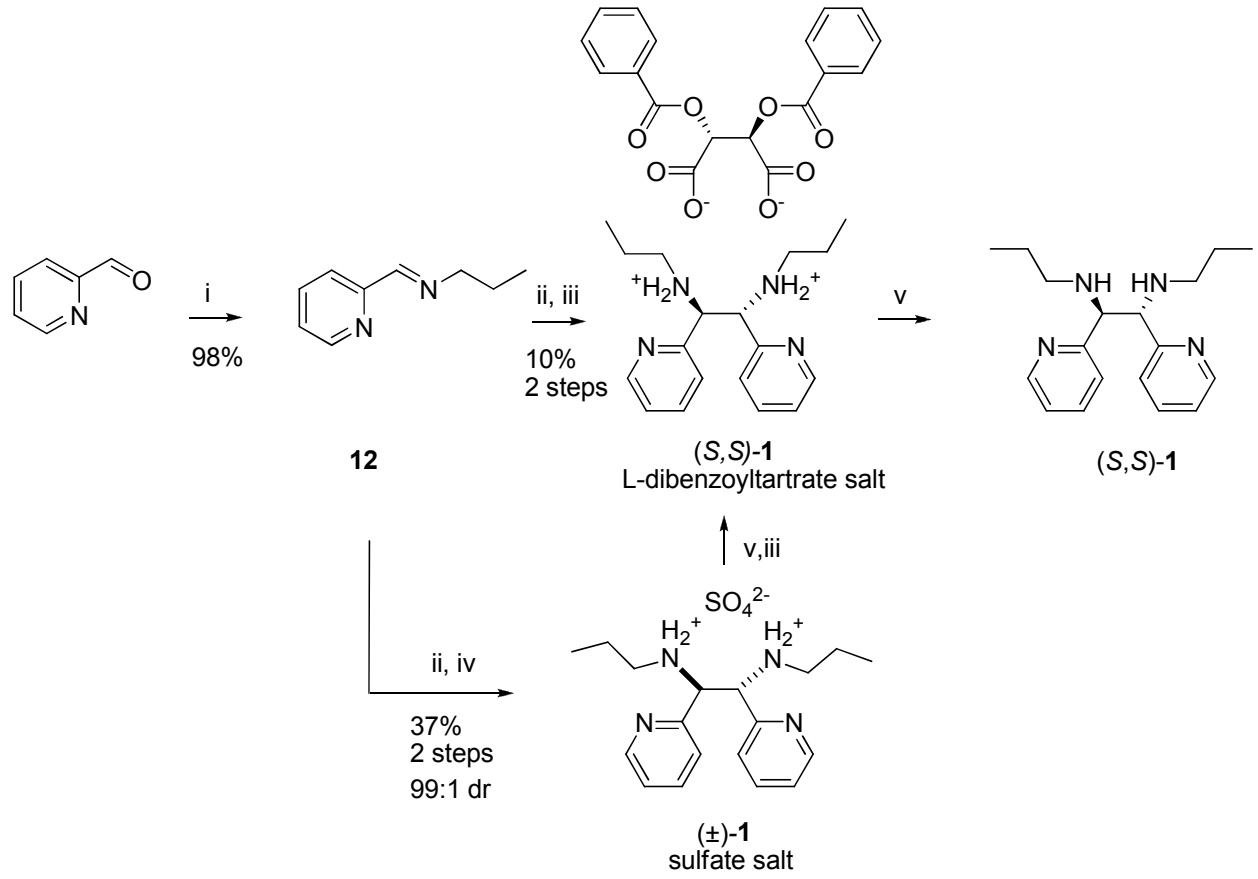
The approach depicted in Scheme 3 was applied starting from 0.5 kg of the 2-pyridinecarboxaldehyde. We were able to obtain 144 g of the diamine (±)-**1** corresponding to an overall yield of 25% from 2-pyridinecarboxaldehyde. No chromatography was necessary in the sequence as the intermediates **8** and **9** both had favorable properties allowing for an efficient crystallization to take place. Furthermore, careful adjustment of pH was used in the extractive work-up of (±)-**1** which raised the chemical purity to an acceptable level.

Despite the successful results obtained above, the approach E still suffers from being a relatively long linear sequence with a low overall yield. Thus, we were eager to see if we could find a route that was shorter allowing for a more efficient synthesis of the desired diamine (*S,S*)-**1**.

APPROACH F.

In a paper by Alexakis et al., they describe the synthesis of various C_2 symmetrical diamines of type **1** mediated by Zn/Me_3SiCl (approach F).2[a] Although the diastereoselectivity in these reactions in most cases were low to moderate resulting in a low yield of the desired isomer after purification, the desired product was obtained in one single step from easily prepared imines. If this method could be successfully applied on imine **12**, only a resolution of the diasteromeric mixture and the enantiomers would remain to reach diamines of type **1**. Therefore, we put some efforts to investigate this approach. The starting imine **12** was easily prepared according to Scheme 4 in almost quantitative yield.

Scheme 4. Approach F[a].



[a]Reaction conditions: (i) 1-propylamine (1.05 eq), EtOH; (ii) Zn powder (0.5 equiv.), TMSCl (1.5 equiv.), CH_3CN, extractive work-up; (iii) (-)-dibenzoyl-L-tartaric acid, CH_3CN, > 99% ee, 98:2 dr; (iv) H_2SO_4, CH_3CN; (v) Extraction with MTBE/NH_3 (aq.) solution.

In a first attempt to reductively couple imine **12**, we found that the crude mixture when analyzed by ^{1}H NMR consisted of a 70:30 mixture of diastereomers which was a slightly better result than that reported for an analogue.2[a] A 41% assay w/w by ^{1}H NMR of the desired isomer was recorded which corresponded to an effective yield of 40%. Although a method exists for the isomerisation of the meso- to the (±)-isomer we believed that this method should not be practical on a large scale.[12] Since we wanted to avoid purification of the crude mixture through chromatography, we searched for a suitable acid that would separate the diasteromers and remove other impurities upon salt formation. A salt screen was set up and we found that sulphuric acid formed the corresponding diastereomerically pure bidentate sulfate salt of (±)-**1** in 37% overall yield. The experiment was repeated on a 1.3 mol scale with similar result. Pure enantiomer (*S,S*)-**1** could be obtained after resolution of the free based racemic diamine (±)-**1** with (-)-dibenzoyl-L-tartaric acid as described above. Encouraged by these results we wanted to investigate if the process could be further improved to allow separation of diastereomers and enantiomeric salt resolution in only one crystallization step. On a small scale, we were delighted to see that after treatment of the crude mixture from the reductive coupling of the imine **12** with (-)-dibenzoyl-L-tartaric acid acid in CH_3CN, both a diastereomeric separation and enantiomeric resolution were observed and the almost stereoisomerically (ee > 99%, dr 98:2) pure (*S*,*S*)-**1** L-dibenzoyltartrate salt was isolated in a 15% overall yield (*i.e.* from 2-pyridinecarboxaldehyde).[13] Through comparison of retention times on chiral HPLC with authentic material prepared from commercially available diamine (*S,S*)-**2** (transformation (*S,S*)-**2** to (*S,S*)-**1**, Scheme 1), we were able to assign the absolute stereochemistry of the diamine **1** as *S,S*.

Before we were ready for further scale-up using this approach we wanted to solve a few issues in the reductive coupling step: First of all, in the original procedure, an excess of Zn (Zn:imine,

1:1) is used which of course led to a large amount of zinc (0) waste after the reaction is complete. This excess of zinc resulted in a more troublesome work-up and the quenching of the excess could also be a potentially hazardous operation. In an attempt to reduce the amount of zinc used we found that a stoichiometry of 1/0.5 (imine/Zn) was enough to reach almost full conversion in the reductive coupling resulting in a simple work-up with no or little remaining unreacted zinc in the reactor. Another issue that had to be addressed before further scale-up work was to remove all zinc salts liberated prior to salt formation because the product diamine (±)-**1** was found to bind zinc very tightly which then interfered in the crystallization step. This was solved through washing of the crude mixture with an EDTA/25% NH_3 solution which efficiently removed all zinc salts and also facilitated the work-up. Another thing that we wanted to avoid prior to further scale-up was the use of the toxic 1,2-dibromoethane used for the activation of the zinc. Fortunately we found that this activation procedure was not necessary as we got the same result using the zinc as such from a fresh bottle. Moreover, the exclusion of 1,2-dibromoethane as activation reagent gave rise to a more straightforward work-up in which the formation of black unwanted precipitates were avoided. However, we noticed that these improvements were at the expense of the diastereoselectivity in the coupling step since now an approximately 60:40 ratio of the two diastereomers were obtained. Using the optimized conditions as described above we were able to produce 77 g of the almost stereoisomerically pure (*S*,*S*)-**1** L-dibenzoyltartrate salt (ee > 99%, dr 98:2) in 10% overall yield from the imine **12**. This was our preferred method among the three main routes (approach D-F) evaluated on a large scale (Table 2).

Table 2. Comparison of the three approaches (D-F) to obtain diamine (±)-**1**.

	Approach D	**Approach E**	**Approach F**
Cost and accessibility of raw materials	+	+	+

Number of steps	7	5	3
Overall yield	22%[a]	25%[b]	34%[c] (10%)[d]
Ease of operation	-	+	+
Highly exothermic steps	Yes	No	No

[a] Overall yield to crude diamine (±)-**1** with assay 74% w/w. [b] Overall yield to crude diamine (±)-**1** with assay 82% w/w. [c] Overall yield to (±)-**1** sulfate salt. [d] Overall yield to (*S*,*S*)-**1** L-dibenzoyltartrate salt.

CONCLUSION

Several routes towards the C_2 symmetrical diamine (*S*,*S*)-**1** have been evaluated, both asymmetric as well as non-asymmetric ones. It turned out that a Zn/TMSCl mediated reductive coupling approach of imine **12** was the preferred method. Despite being non-asymmetric and also low yielding this route was chosen for further scale-up. This is for reasons as follows: It is a short and simple sequence to execute on a large scale and the pure desired enantiomer can easily be isolated after a single salt crystallization. Moreover, the methods are chromatography free processes and the cost of raw materials is very low. The obtained C_2 symmetrical diamine (*S*,*S*)-**1** can be used as a building block to synthesize new potent ion channel blockers. The diamine might also be useful as a chiral ligand in asymmetric syntheses.

EXPERIMENTAL SECTION

General. All materials were purchased from commercial suppliers and used as such without further purification. Zinc was supplied from Sigma-Aldrich (powder, < 10 µm, cat. no. 20998-8). The reactions were performed under an atmosphere of nitrogen in reactors equipped with overhead stirrer and connected to an external heating Huber aggregate. In process controls (IPCs) were recorded using either HPLC or ^{1}H NMR analyses on the crude mixtures. Diastereomeric ratios were determined using ^{1}H NMR integration. Assays of final products and crude mixtures

were determined by ^{1}H NMR integration using either benzylbenzoate or octamethylcyclotetrasiloxane as internal standards. Enantiomeric purity of compound (*S,S*)-**1** was determined by chiral HPLC analysis (column Chiralpak IA, 250 x 4.6 mm, eluent heptane/2-propanol/Et_3N 70/30/0.1). High resolution mass spectrometry was performed on a Waters XEVO qTOF instrument, mass precision ± 5 ppm. NMR measurement was performed on a Bruker Avance III spectrometer. LC/MS analyses were recorded on a Waters ZMD instrument, LC column Terra MS C_8 (Waters); detection with a HP 1100 MS-detector diode array.

1,2-Di(pyridin-2-yl)ethane-1,2-dione (4). A reactor was charged with 1,2-di(pyridin-2-yl)ethene-1,2-diol **3** (2.68 Kg, 12.5 mol), sodium acetate (2.26 Kg, 27.5 mol) and EtOH (6.0 L). To the resulting suspension was added over 2.5 h a solution of I_2 (3.17 Kg, 12.5 mol) in EtOH (20 L) at 20 °C. The stirring was continued at 20 °C for 20 min. Then, 5% aqueous $Na_2S_2O_3$ (800 mL) was added. 20 L of the solvent was distilled off at 30 - 40 mbar with the mantle temperature set at 40 °C. The suspension was further stirred at 20 °C for an additional 1 hour. The product was filtered off and washed with cold EtOH (2 x 5 L). The solid product was dried under reduced pressure to yield **4** (1.96 Kg, 100% w/w, 9.24 mol) as a white solid. ^{1}H NMR was in accordance with that previously published.[14]

2,3-Di(pyridin-2-yl)-1,4-diazaspiro[4.5]deca-1,3-diene (5). A reactor was charged with **4** (1.96 Kg, 9.24 mol), ammonium acetate (5.70 Kg, 73.9 mol), cyclohexanone (1.24 L, 12.0 mol) and AcOH (9.3 L). The resulting mixture was stirred at 40 °C for 17 hours. Water (18.5 L) and CH_2Cl_2 (7 L) were added. The phases were separated and the aqueous layer extracted with CH_2Cl_2 (8 L). The combined organic layers were washed with 3.8M NaOH (18.5 L) and water (4 L). The organic layer was concentrated to yield crude **5** (2.70 kg, assay 60% w/w, 5.57 mol) as a brown syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67–2.01 (m, 10H), 7.27 (ddd, J = 7.5, 4.8, 1.3

Hz, 2H), 7.74 (dt, *J* = 7.5, 1.7 Hz, 2H), 7.80 (dt, *J* = 7.8, 1.2 Hz, 2H), 8.46 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 25.5, 34.2, 105.2, 123.8, 124.0, 136.3, 148.7, 152.3, 163.6. HRMS (ESI+) m/e 291.1626 [$(M + H)^+$, calcd for $C_{18}H_{19}N_4$ 291.1610].

(±)-1,2-Di(pyridin-2-yl)ethane-1,2-diamine dihydrochloride [(±)-2 x 2HCl]. A mixture of **5** (2.69 kg, 60% w/w, 5.56 mol) in MeOH (10 L) was stirred in a 25 L reactor. Magnesium turnings (40 g, 1.65 mol), and I_2 (2.7 g, 10 mmol) were added which resulted in gas evolution and an exothermic reaction. More magnesium turnings were added in 75 – 100 g portions over 7 hours (500 g, 20.6 mol). The temperature of the reaction mixture was maintained in the interval 27 – 40 °C controlled by the rate of addition of the magnesium and adjustment of the mantle temperature. After complete addition of the magnesium, the mantle temperature was set at 25 °C and the stirring was continued for an additional 14 hours. The resulting mixture of crude **6** was cooled to 15 °C and 5.6M HCl in 2-propanol (10.9 L, 61 mol) was added over 2 hours. The resulting suspension was stirred at 20 °C for 21 hours. A second portion of MeOH (5 L) was added and stirring was continued at 20 °C for 4 days. The solid product was filtered off, washed with MeOH (3 x 2.5 L) and dried under reduced pressure to yield (±)-**2** x 2HCl (1.24 kg, 87% w/w, 3.76 mol) as an off-white solid. ^{1}H NMR (400 MHz, D_2O): δ 4.89 (s, 2H), 7.16 (dt, *J* = 7.9, 1.0 Hz, 2H), 7.30 (ddd, *J* = 7.7, 4.9, 1.1 Hz, 2H), 7.66 (dt, *J* = 7.8, 1.8 Hz, 2H), 8.45 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 2H).

(±)-N1,N2-Dipropyl-1,2-di(pyridin-2-yl)ethane-1,2-diamine [(±)-1]. A reactor was charged with $NaBH(OAc)_3$ (763 g, 3.60 mol) and CH_2Cl_2 (4 L). The mantle temperature was set at 20 °C and DIPEA (836 mL, 4.80 mol) was added followed by the addition of propionaldehyde (871 mL, 12.0 mol). A solution of (±)-**2** x 2HCl (396 g, 87% w/w, 1.20 mol) and DIPEA (836 mL, 4.80 mol) in CH_2Cl_2 (10 L) was added over 30 minutes and the stirring continued for 1 hour.

Water (2.0 L) and 3.8M HCl (6 L) were added to the resulting crude mixture of compound **7** over 35 minutes and the stirring continued for 30 minutes. To the aqueous layer was added 1-propanethiol (650 mL, 7.18 mol). The resulting mixture was stirred at 60 °C for 4 hours and at 20 °C for an additional 5 hours. The mixture was washed with CH_2Cl_2 (2 x 5 L). To the aqueous layer was added over 40 minutes a solution of 3.8M NaOH (10 L). The resulting emulsion (pH11) was heated to 30 °C and extracted with CH_2Cl_2 (3 x 2.5 L). The combined organic layers were concentrated to yield the diamine (±)-**1** (394 g, 74% w/w, 0.977 mol) as a brown oil. The NMR and MS data were in accordance with those given for (*S*,*S*)-**1** below.

N-(Pyridin-2-ylmethylene)propan-1-amine (12). With a temperature set at 0 ^{o}C, the reactor was charged with propan-1-amine (318 g, 5.37 mol) and EtOH (99.5%, 2 L). 2-pyridinecarboxaldehyde (548 g, 5.12 mol) was added over a 15 minute period keeping the temperature between + 8 to + 23 ^{o}C (exothermic). The brown homogenous solution was stirred for 14 hours[15] and then concentrated at 40 ^{o}C. Traces of water were azeotropically removed with toluene (3 X 200 ml) to give **12** as a dark brown liquid (744 g, 96% w/w, 4.82 mol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.72-1.82 (m, 2H), 3.65 (dt, *J* = 6.9, 1.2 Hz, 2H), 7.29-7.33 (m, 1H), 7.71-7.77 (m, 1H), 7.98-8.02 (m, 1H), 8.37-8.39 (m, 1H), 8.64-8.67 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.8, 23.8, 63.3, 121.1, 124.5, 136.4, 149.4, 154.7, 161.7.

(±)-N,N'-Dipropyl-1,2-di(pyridin-2-yl)ethane-1,2-diammonium sulphate [(±)-1 sulfate salt]. A mixture of zinc (< 10 μM , 91g, 1.39 mol) and dibromoethane (12.4 g, 66 mmol) in acetonitrile (2 L) was heated at reflux for 5 minutes. At 28 ^{o}C, chlorotrimethylsilane (7.2 g, 0.066 mol) was added within 1 minute and stirred for 30 minutes at 28 ^{o}C. The mantle temperature was set at 20 ^{o}C and N-(pyridin-2-ylmethylene)propan-1-amine **12** (209 g, 96% w/w, 1.35 mol) was added within 10 minutes. The reaction temperature was maintained in the

interval + 27 to + 30 ^{o}C during this addition. After 5 minutes of stirring, chlorotrimethylsilane (216 g, 1.99 mol) was added within 20 minutes keeping the temperature between +27 and +31 °C (exothermic!). The green-brown suspension was then stirred at ambient temperature for 35 minutes. The mixture was cooled to + 1 ^{o}C and the reaction is then carefully quenched (exothermic!) through the addition of a solution of 25% NH_3 solution (aq., 2 L) keeping temperature below 20 ^{o}C. MTBE (2.5 L) was added and the biphasic mixture was stirred for 15 minutes followed by separation of the layers. The dark brown organic layer was concentrated to a viscous oil. To this was added MTBE (1 L) and 0.27M EDTA solution (disodium salt, 1 L) followed by the addition of 25% NH_3 solution (0.5 L). The biphasic mixture was stirred for 18 hrs followed by separation of the layers. The dark brown organic layer was washed with a mixture of 0.27M EDTA solution (disodium salt, 0.5 L) + 25% NH_3 solution (aq, 250 ml). The pooled aqueous layer was extracted with MTBE (0.5 L). The pooled organic layer was concentrated to give the crude diamine as a viscous oil (181 g, 41% w/w of the desired isomer by ^{1}H NMR, diastereomeric ratio 70/30, 0.249 mol). The crude oil was dissolved in acetonitrile (900 mL) and sulfuric acid (45.5 g, 0.46 mol) was added. The green suspension obtained was heated to reflux and the suspension was then allowed to reach 20 ^{o}C during 1 hour and then stirred at that temperature for an additional 1 hour. The thick green suspension was filtered and washed with CH_3CN (5 X 100 mL). After drying under reduced pressure the desired (±)-**1** sulfate salt was obtained as a pale green solid (107 g, 90% w/w, 0.243 mol, dr ~ 99:1) with CH_3CN as the main impurity (7% w/w). ^{1}H NMR (400 MHz, DMSO) δ 0.81 (t, J = 7.4 Hz, 6H), 1.41-1.61 (m, 4H), 2.42-2.64 (m, 4H), 4.34 (s, 2H), 6.93-6.96 (m, 2H), 7.25-7.29 (m, 2H), 7.56-7.61 (m, 2H), 8.56-8.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 20.8, 48.0, 65.0, 123.5, 124.3, 136.8, 149.5, 155.2.

(1*S*,2*S*)-N1,N2-Dipropyl-1,2-di(pyridin-2-yl)ethane-1,2-diamine (-)-dibenzoyl-L-tartrate salt [(*S*,*S*)-1 L-dibenzoyltartrate salt]. The reactor was charged with zinc (< 10 μm, 71.4 g, 1.09 mol) followed by the addition of acetonitrile (2.5 L). Mantle temperature was set at 20 ^{o}C and (E)-N-(pyridin-2-ylmethylene)propan-1-amine **12** (337 g, 96% w/w, 2.18 mol) was added within 4 minutes. No exotherm was observed. Chlorotrimethylsilane (356 g, 3.27 mol) was added during 40 minutes while maintaining the reaction temperature between + 23 to 30 ^{o}C. A green suspension was obtained which was further stirred at ambient temperature for 30 minutes. ^{1}H NMR analysis of the crude mixture indicated full conversion of the imine. The mantle temperature was set at 0 ^{o}C and an aqueous solution of 25% NH_3 solution (1 L) was added during 10 minutes. CAUTION: The reaction is initially exothermic! The reaction temperature was kept below + 39 ^{o}C during this addition. MTBE (2.5 L) was added and the biphasic mixture was stirred for 1 hour. The pale yellow aqueous layer was discarded and the dark brown organic layer was concentrated to almost dryness. The residue was dissolved in MTBE (1 L). An aqueous solutions of EDTA (disodium salt, 0.27M, 1.5 L) + 25% NH_3 solution (aq., 250 mL) were added and the biphasic mixture was stirred over night. The aqueous dark green layer was discarded. The organic layer was washed with water (500 mL) followed by concentration to a dark brown oil (326 g, 35% w/w of the desired isomer, 0.382 mol). Water was azeotropically removed with MTBE (3 X 200 mL). The crude oil was dissolved in acetonitrile (2 L). The mixture was heated to 55 ^{o}C and (-)-dibenzoyl-L-tartaric acid (196 g, 0.55 mol) was added in small portions. The dark brown homogenous solution was then allowed to attain 20 ^{o}C during 1 hour. The thin suspension obtained was further stirred at room temperature for 4 hours. The mixture was then filtered and the salt collected was washed with CH_3CN (5 x 150 mL). After drying under reduced pressure, the titled compound was obtained as a pale green solid (77 g, 97% w/w, 114 mmol), dr

98:2 by ^{1}H NMR, ee > 99% by chiral HPLC. ^{1}H NMR (400 MHz, DMSO) δ 0.76 (t, *J* = 7.4 Hz, 6H), 1.35-1.55 (m, 4H), 2.36-2.44 (m, 2H), 2.48-2.56 (m, 2H), 4.28 (s, 2H), 5.67 (s, 2H), 6.96-6.99 (m, 2H), 7.20-7.24 (m, 2H), 7.46-7.65 (m, 8H), 7.91-7.95 (m, 4H), 8.50-8.53 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 11.2, 20.8, 47.8, 65.2, 72.3, 123.2, 124.1, 128.7, 129.3, 129.6, 133.4, 136.5, 149.3, 155.7, 164.9, 168.1.

(1*S*,2*S*)-N1,N2-Dipropyl-1,2-di(pyridin-2-yl)ethane-1,2-diamine (*S*,*S*)-1. An analytical sample was prepared from the above (*S*,*S*)-**1** L-dibenzoyltartrate salt through extraction with MTBE/NH_3 (aq) solution followed by concentration of organic layer to a pale yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.4 Hz, 6H), 1.38-1.51 (m, 4H), 2.31-2.41 (m, 4H), 3.86 (s, 2H), 6.89-6.92 (m, 2H), 6.97-7.01 (m, 2H), 7.34-7.39 (m, 2H), 8.45-8.47 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.8, 23.4, 50.0. 69.3, 121.7, 123.4, 135.5, 149.2, 161.6. HRMS (ESI+) m/e 299.2246 [$(M + H)^+$, calcd for $C_{18}H_{27}N_4$ 299.2236]. $[\alpha]_D^{20}$ – 1 (c = 1, CH_3CN), dr 98:2, ee > 99%.

***Cis*-(±)-2,2',2''-(4,5-dihydro-1*H*-Imidazole-2,4,5-triyl)tripyridine (8).** A solution of 2-pyridinecarboxaldehyde (500 g, 4.67 mol) in THF (3 L) was heated to 50 ^{o}C and a solution of ammonia (aq., 26% w/w, 0.92 L, 12.6 mol) was added within 5 minutes. The homogenous brown solution was then stirred at 50 ^{o}C for 3 days. The mixture was cooled to 20 ^{o}C, 30% brine (1.4 L) was added and the phases were separated. The organic phase was concentrated to a dark brown solid. Water was azeotropically removed with toluene (3 x 300 mL). To the crude solid was added CH_2Cl_2 (400 mL) and isopropyl acetate (1000 mL). The brown suspension was then allowed to stir over night followed by cooling at 0 ^{o}C for 30 minutes. The mixture was filtered and the solid was washed with isopropyl acetate (500 mL). After drying under reduced pressure,

the titled compound was obtained as a beige solid (305 g, 98% w/w, 0.99 mol). Analytical data was in accordance with those given in the literature.[7]

***Trans*-(±)-2,2',2''-(4,5-dihydro-1*H*-Imidazole-2,4,5-triyl)tripyridine (9).** Compound **8** (305 g, 98% w/w, 0.99 mol) was suspended in dry THF (1 L) and a solution of potassium 2-methylbutan-2-olate (1.7M in THF, 12 mL, 20 mmol) was added within 1 minute. The mixture was stirred for 1.5 hour after which ^{1}H NMR analysis of the crude mixture indicated 96% conversion to the desired trans-isomer. Heptane (100 mL) and seeding crystals were sequentially added. An immediate and quite rapid crystallization initiated. The thin suspension was stirred at 20 ^{o}C for 30 minutes. More heptane (1 L) was added and the beige suspension was stirred over night. The mixture was filtered and the solid collected was washed with MTBE (3 x 200 mL). After drying under reduced pressure the title compound was obtained as a beige solid (268 g, 98% w/w, 0.87 mol). Analytical data were in accordance with those given in the literature.[7]

***Trans*-(±)-2,2',2''-(imidazolidine-2,4,5-triyl)tripyridine (10).** Compound **9** (268 g, 98% w/w, 0.87 mol) and acetic acid (255 ml, 4.45 mol) were mixed in 2-methyl-THF (4.0 L). The suspension was heated to 40 ^{o}C and zinc (< 10 μm, 70 g, 1.07 mol) was added over a 10 minute period. The mixture was stirred for 2 days after which full conversion of the starting material had been obtained (^{1}H NMR). The mixture was cooled to 10 °C and a solution of sodium hydroxide (3.75 M, 2.0 L, 7.5 mol) was added. The two-phase mixture was stirred for 15 minutes followed by removal of the inhomogenous aqueous layer. To the organic layer was added a solution of EDTA (aq., 0.26 M, 1.2 L). The pH was adjusted to 8.9 using sodium hydroxide solution (aq., 3.75 M, 85 mL). The aqueous phase was discarded. The organic layer was washed with brine (500 mL) followed by concentration of the clear organic layer. The residue was concentrated with 2 x 200 ml 2-methyl-THF to give the product as a red oil (255 g, 80% w/w, 0.67 mol).

HRMS (ESI+) m/e 304.1570 [$(M + H)^+$, calcd for $C_{18}H_{17}N_5$ 304.1557]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.52 (d, *J* = 6.7 Hz, 1H), 4.55 (d, *J* = 6.7 Hz, 1H), 5.41 (s, 1H), 7.15 – 7.19 (m, 2H), 7.21 (d, *J* = 7.8 Hz, 1H) 7.24 – 7.28 (m, 2H), 7.54 – 7.63 (m, 3H), 7.72 (dt, *J* = 7.5, 1.2 Hz, 1H), 8.62 (m, 2H), 8.67 (d, *J* = 4.8 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.22, 159.35, 159.19, 149.47, 149.45, 149.45, 149.37, 136.63, 136.30, 136.27, 129.01, 128.20, 125.28, 123.28, 123.13, 122.71, 122.40, 122.11, 122.07, 78.69, 72.00, 70.02.

***Trans*-(±)-2,2',2''-(1,3-dipropylimidazolidine-2,4,5-triyl)tripyridine (11)**. Propionaldehyde (195 g, 3.36 mol) and DIPEA (348 g, 2.70 mol) were added to a solution of **10** (255 g, 80% w/w, 672 mmol) in ethyl acetate (3.0 L). At 18 °C sodium triacetoxyborohydride (364 g, 1.72 mol) was added portion wise over a period of 40 minutes. The reaction is slightly exothermic and the temperature rose to 26 °C during the addition. The mixture was stirred for 16 hrs at 20 °C. The reaction was quenched by the addition of water (1 L) after which a rise in temperature from 20 to 29 °C was noticed. After stirring for 4 minutes the phases were separated and the organic phase was washed with another 600 ml of water. The resulting solution was used as such in the next step. An assay showed 69% effective yield[16]. A small aliquot was concentrated and used for recording of the NMR spectra. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.56 (dt, *J* = 7.4, 3.3 Hz, 6H), 1.05 – 1.26 (m, 4H), 1.99 – 2.12 (m, 2H), 2.72 – 2.86 (m, 2H), 4.33 (d, *J* = 5.4 Hz, 1H), 4.54 (d, *J* = 5.4 Hz, 1H), 5.19 (s, 1H), 7.11 – 7.17 (m, 2H), 7.19 – 7.26 (m, 1H), 7.39 – 7.46 (m, 1H), 7.61 – 7.79 (m, 3H), 7.9 – 7.98 (m, 2H), 8.4 – 8.45 (m, 1H), 8.5 – 8.58 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.80, 163.38, 160.85, 149.26, 148.67, 148.16, 136.59, 136.34, 136.24, 123.80, 123.18, 122.81, 122.24, 122.07, 121.80, 87.73, 76.24, 73.89, 55.76, 48.09, 22.27, 20.95, 11.72, 11.68.

(±)-N1,N2-Dipropyl-1,2-di(pyridin-2-yl)ethane-1,2-diamine [(±)-1]. To 3.7 L of the extraction mixture containing **11** from the previous step (465 mmol) was added 390 ml 12 M hydrochloric acid. The mixture was stirred for 5 minutes followed by separation of the layers. To the aqueous layer was added 1-propanethiol (253 ml, 6 eq) and the mixture was heated at 50 °C for 18 hrs. MTBE (900 ml) was added and the pH was adjusted to 5.95 using 3.8 M sodium hydroxide. The aqueous layer was washed with 900 ml of MTBE. The pH of the aqueous layer was adjusted to 12.3 by addition of 200 mL of 3.8 M sodium hydroxide solution and then extracted with 900 ml MTBE. The organic layer was washed with 100 ml of water and then filtered through celite (Celpure C300). After concentration, the desired product (±)-**1** was obtained as an oil (143.8 g, 82% w/w, 0.395 mol). Spectroscopic data were in accordance with those given for (*S*,*S*)-**1** above.

ASSOCIATED CONTENT

Supporting Information. ^{1}H NMR, ^{13}C NMR, HRMS, optical rotation, and HPLC analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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[11] In order to avoid the risk of acylation of the amines by the EtOAc we later on changed solvent to CH_3CN (see approach F).

[12] Alexakis, A.; Aujard, I.; Mangeney, P. *Synlett* **1998**, 875-876.

[13] It was found that heating the salt in CH_3CN at reflux for several hours, resulted in deterioration.

[14] Rakotomalala, M; Katz, M; Voisin, E; Pace, T. C. S; Bohne, C.; Williams, V. E. *Can. J. Chem.* **2011**, *89*, 297-302.

[15] By ^{1}H NMR full conversion of the aldehyde was indicated after 1 hr.

[16] By HPLC-MS the material contains 8% of the pyridine/propyl transaminalized product, **7**, (m+1 = 339). The assay given corresponds to the sum of **7** and **11**.