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Asymmetric Synthesis of (*S*)-Mirtazapine: Unexpected Racemization through an Aromatic *ipso*-Attack Mechanism

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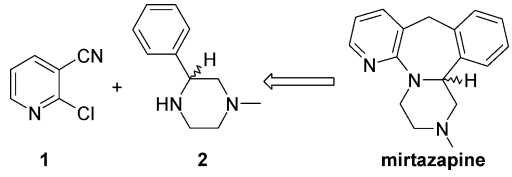
An asymmetric synthesis of (*S*)-mirtazapine has been achieved from the synthesis of the racemate by using (*S*)-1-methyl-3-phenylpiperazine as the starting material. Unfortunately, significant racemization was encountered in the final step, which involved an electrophilic aromatic ring closure of a alcohol by concentrated sulfuric acid. A significantly higher *ee* was observed when polyphosphoric acid (PPA) was used instead. A remarkable correlation between the amount of PPA used and the *ee* of the product was revealed, namely, an increase in the *ee* upon decreasing the amount of PPA. This trend was paralleled by the formation of an increasing amount of a side-product upon lowering the amount of PPA. The racemization and formation of a side-product can be explained by an *ipso*-attack mechanism during the electrophilic aromatic ring-closure reaction. This mechanism was supported by a mechanistic study using a deuterium-labeled substrate.

Introduction

Mirtazapine is a tetracyclic compound that as a racemate finds widespread use in the treatment of depression. The synthesis of mirtazapine has mainly been covered in patents.[1–3] In addition, the synthesis of tritium-, carbon-13-, and carbon-14-radiolabelled mirtazapine has been described in literature.[4] The biological effects of mirtazapine have been comprehensively reviewed over the past two decades.[5,6] Investigations into the biological effects of the enantiomers of mirtazapine revealed interesting properties of the compound in its pure enantiomeric form,[7] for example, the (*S*) enantiomer has demonstrated potential in the treatments of insomnia and the climacteric symptoms associated with the menopause. In order to obtain (*S*)-mirtazapine in sufficient quantities to start pharmaceutical and clinical development, a classical process for the resolution of the enantiomers of the readily available mirtazapine was developed. This process, employing dibenzoyl-D-tartaric acid as the resolving agent, has been used to manufacture over 1300 kg of (*S*)-mirtazapine maleate in a batch scale up to 250 kg.

The resolution process is, however, inherently associated with a 65% loss of mirtazapine and with the formation of large amounts of waste. For the commercial manufacture of (*S*)-mirtazapine maleate this process is thus not an economically or environmentally benign option. This has triggered the search for an asymmetric synthesis of (*S*)-mirtazapine. It would be particularly interesting to see if an asymmetric synthesis could be deduced from the synthesis of racemic mirtazapine, which starts with 2-chloro-3-cyanopyridine (**1**) and 1-methyl-3-phenyl-piperazine (**2**), as shown in Scheme 1.[1] It was anticipated that the chiral centre of (*S*)-mirtazapine could be introduced via the 1-methyl-3-phenylpiperazine building block and consequently the use of enantiopure (*S*)-1-methyl-3-phenylpiperazine in the synthesis of mirtazapine should in principle lead to a viable stereoconvergent synthesis of (*S*)-mirtazapine.



Scheme 1. Retrosynthesis of mirtazapine.

This paper describes the efforts to develop an asymmetric synthesis of (*S*)-mirtazapine starting from 2-chloro-3-cyanopyridine (**1**) and (*S*)-1-methyl-3-phenylpiperazine [(*S*)-**2**]. In addition, the mechanistic aspects of an unexpected racemization are revealed.

Results and Discussion

In order to obtain significant quantities of (*S*)-1-methyl-3-phenylpiperazine [(*S*)-**2**] for use in the synthesis of (*S*)-mirtazapine, a classical resolution using (*S*)-(+)-Anicyphos

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was exploited (see Figure 1).[8] From a series of resolving agents, this compound appeared the most effective. First the salt of (*S*)-**2** with (*S*)-(+)-Anicyphos was crystallized from water. The free base of (*S*)-**2** was liberated by treatment with sodium hydroxide and extraction with ethyl acetate. In this way (*S*)-**2** was obtained in an overall yield of between 35–40% and with an *ee* >98%. This process has been applied to the preparation of more than a kg of this optically active building block. Although by this process 65% of 1-methyl-3-phenylpiperazine **2** was lost, from an economic point of view, this is preferred over resolution of mirtazapine as the latter is a compound with significantly more added value. Moreover, several alternative routes to (*S*)-1-methyl-3-phenylpiperazine have been discovered. One of these proceeds by enzymatic resolution of the oxalamate derivative of the racemic mixture.[9] In addition, a number of stereoconvergent synthetic routes starting from (*S*)-phenylglycine have been elaborated of which one is shown in this paper (see Scheme 4).[10]

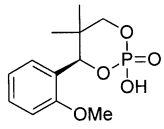
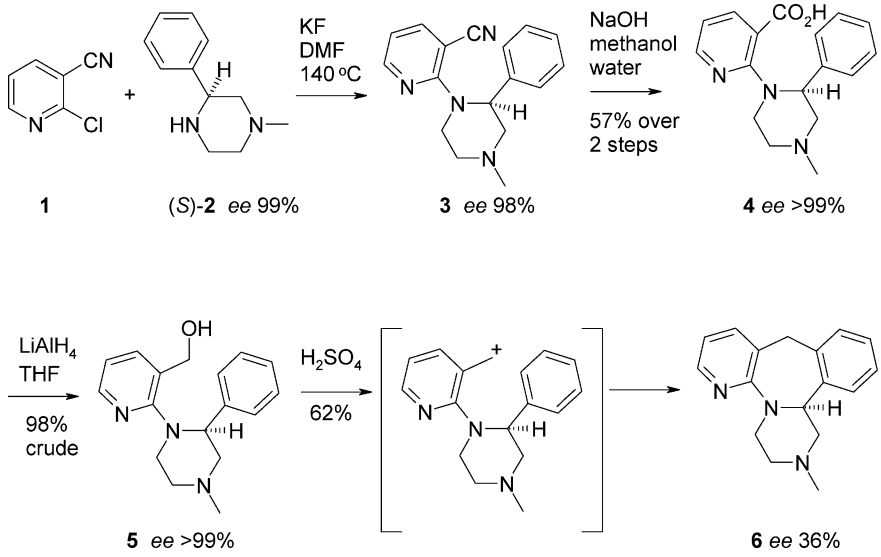


Figure 1. Structure of (*S*)-(+)-Anicyphos.

The optically active (*S*)-1-methyl-3-phenylpiperazine (*S*)-**2** was used in the synthesis of (*S*)-mirtazapine, which is depicted in Scheme 2. The first step involves coupling of (*S*)-**2** and 2-chloro-3-cyanopyridine (**1**) in boiling DMF using potassium fluoride to facilitate the nucleophilic aromatic substitution. During this reaction no loss of optical purity was found and the nitrile **3** was directly converted into carboxylic acid **4** by treatment with sodium hydroxide in a mixture of methanol and water. After crystallization, the acid **4** was obtained in a yield of 57% and with an *ee* > 99%. Reaction of carboxylic acid **4** with lithium aluminium hydride furnished cleanly and in excellent yield alcohol **5**. In the last step, alcohol **5** was treated with concentrated sulfuric acid and the thus formed cation underwent electrophilic aromatic substitution at the phenyl ring. Disappointingly, a considerable loss in enantiomeric excess was observed in this last step as the *ee* of (*S*)-mirtazapine (compound **6**) was found to be only 36%.

It was demonstrated that (*S*)-mirtazapine is enantiostable in concentrated sulfuric acid and thus the observed racemization had to be related to the mechanism of the electrophilic ring-closing reaction. However, the mechanism of the racemization was totally unclear and it was presumed that the cation was not entirely enantiostable. In case the racemization takes place in the cation, its possible stabilization by using coordinative solvents could result in an improved enantiopurity of the product. It can be seen from Table 1 that when a noncoordinating solvent like dichloromethane was used (entry 2), the *ee* of the process did not improve. On the other hand when coordinating solvents like alcohols or carboxylic acids were used (entries 3–7) there was a strong positive effect on the enantiopurity, leading to values twice as high, that is, 60–70%. Nevertheless, an *ee* of 60–70% is still insufficient for a viable asymmetric synthesis. A series of different conditions, known for their ability to accomplish dehydration reactions, were investigated (Table 1 entries 8–17). Surprisingly, a considerably higher *ee* was obtained when phosphorus pentoxide was used even with the noncoordinating solvent xylene. More remarkable was the finding that when phosphorus pentoxide was used in combination with the polar solvents DMF or *N*-methylpyrrolidinone (NMP) no racemization was observed at all. As the reaction mixtures with phosphorus pentoxide were very sticky and therefore difficult to stir, a liquid analogue of phosphorus pentoxide, namely polyphosphoric acid, was used instead. The use of only polyphosphoric acid (PPA)[11]



Scheme 2. Synthesis of (*S*)-mirtazapine.

(entry 13) also resulted in a higher *ee* than was obtained with sulfuric acid. When PPA was used with the polar coordinating solvents DMF or NMP (entries 14 and 15) no loss of *ee* was observed, as was the case for phosphorus pentoxide.

Table 1. Effect of various reaction conditions on the *ee* of the electrophilic ring-closure step.

Entry	Acid (anhydride)	Solvent	% *ee*
1	H_2SO_4	–	36
2	H_2SO_4	CH_2Cl_2	36
3	H_2SO_4	EtOH	67
4	H_2SO_4	MeOH	57
5	H_2SO_4	ethylene glycol	57
6	H_2SO_4	acetic acid	57
7	H_2SO_4	acetic anhydride	70
8	$MeSO_3H$	–	55
9	$MeSO_3H$	dibutyl ether	75
10	P_2O_5	xylene	70
11	P_2O_5	DMF	>99
12	P_2O_5	NMP	>99
13	PPA	–	73
14	PPA	DMF[a]	>99
15	PPA	NMP[b]	>99
16	PPA	dibutyl ether[c]	77
17	PPA	H_3PO_4[d]	80

[a] 6–60 volumes of DMF per gram of starting material. [b] 1–60 volumes of NMP per gram of starting material. [c] 2 volumes of dibutyl ether per gram of starting material. [d] 3–5 volumes of phosphoric acid (85%) per gram of starting material.

The ring-closure reaction with PPA was studied in more detail. When the amount of PPA relative to alcohol **5** was varied, a remarkable trend was revealed. The data in Table 2 show that the enantiomeric excess of the product increased upon decreasing the amount of PPA (entries 1–7). Whereas with 30 wt.-equiv. of PPA the enantiomeric excess of the product was only 73%, with 2 wt.-equiv. complete retention of the *ee* was observed. Unfortunately there was a flip side to this discovery. Upon decreasing the amount of PPA, a side-product was formed in increasing amounts and in up to 8% yield when 2 wt.-equiv. of PPA were used. A similar series of experiments was carried out with the oxalate salt of alcohol **5** (entries 8–12) that showed the same trends, that is, an increase in the *ee* of the product paralleled by an increasing amount of an impurity. It should be noted that a number of other impurities were formed as well but the impurity referred to in Table 2 predominates.

The data in Table 2 suggest a relationship between the mechanism of the racemization and the mechanism involved in the formation of the impurity. More precisely, it seems that the path leading to racemization at higher dilutions in PPA, that is, with a large excess of PPA, is being blocked by a pathway leading to the predominant impurity. The structure of the impurity was elucidated and is shown in Figure 2. Both the racemization and the side-product formation can be explained by the mechanism shown in Scheme 3. It is conceivable that besides *ortho* attack an *ipso* attack of the cation **7** at the phenyl ring could also take

Table 2. Effect of the amount of PPA on the *ee* of the product.

Entry	Equiv. PPA (m/m)	% *ee*	Impurity (a/a%)[a]
1	30	73	n.d.
2	19	76	n.d.
3	5	81	n.d.
4	4	82	0.3
5	3	91	1.8
6	2.5	95	2.1
7	2	99	6–8
8	4[b]	83	n.d.
9	2.3[b]	99	6.6
10	2.1[b]	99	7.7
11	2[b]	99	8.4
12	1.6[b]	99	10

[a] Determined by GC relative to the peak of (*S*)-mirtazapine. [b] The oxalate salt of the alcohol **5** was used.

place leading to intermediate **8**. After breaking of the C–C bond with the piperazine ring, the stabilized achiral piperazine cation **9** is formed. Cation **9** could attack the phenyl ring, which, after loss of a proton, would lead to racemic mirtazapine. Alternatively, cation **9** can be intercepted by a nucleophile, for example, a phosphate group or a nucleophilic solvent.[12] This would lead to cyclic N,O-acetal-like compound **10**. Because N,O-acetals are generally not very stable, under the rather harsh reaction conditions compound **10** decomposes in a number of steps to the side-product shown in Figure 2. Quantitatively, the amount of side-product observed under conditions in which racemization is prevented (Table 2, entries 7, 9, 10, 11, and 12; 8–10% of side-product) is not the same as the amount of racemization at higher dilutions (Table 2, entry 1; 27% racemization). This can be explained by other nonidentified side-products that are formed in smaller amounts by the interception of the same piperazine cation intermediate **9**. The compound shown in Figure 2 and referred to in Table 2 as the side-product predominates, and was formed in such amounts that it could be isolated. The effect of the amount of PPA relative to the alcohol on the enantiomeric excess of the product and on the amount of side-product formation can also be explained by this mechanism. In highly diluted reaction mixtures, that is, with a large excess of PPA, the medium is very acidic and thus not very nucleophilic. Presumably, under these conditions, the longevity of the piperazine cation is sufficient to re-attack the phenyl ring thereby forming racemic mirtazapine. Conversely, with smaller amounts of PPA, due to the basic nature of the starting material, the medium is more nucleophilic such that the piperazine cation is intercepted completely and the path towards racemization is blocked.

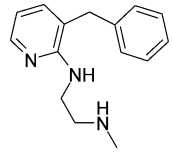
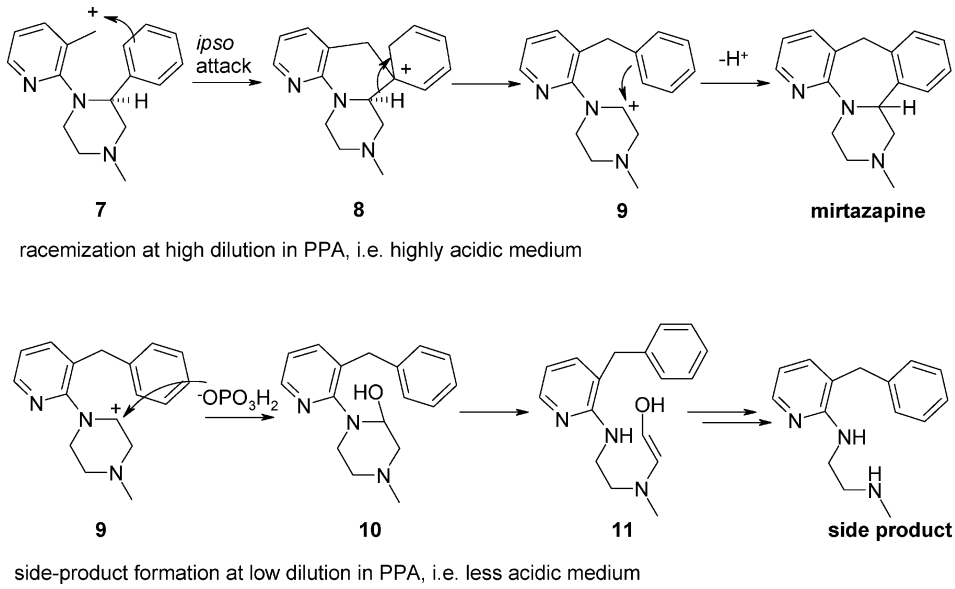


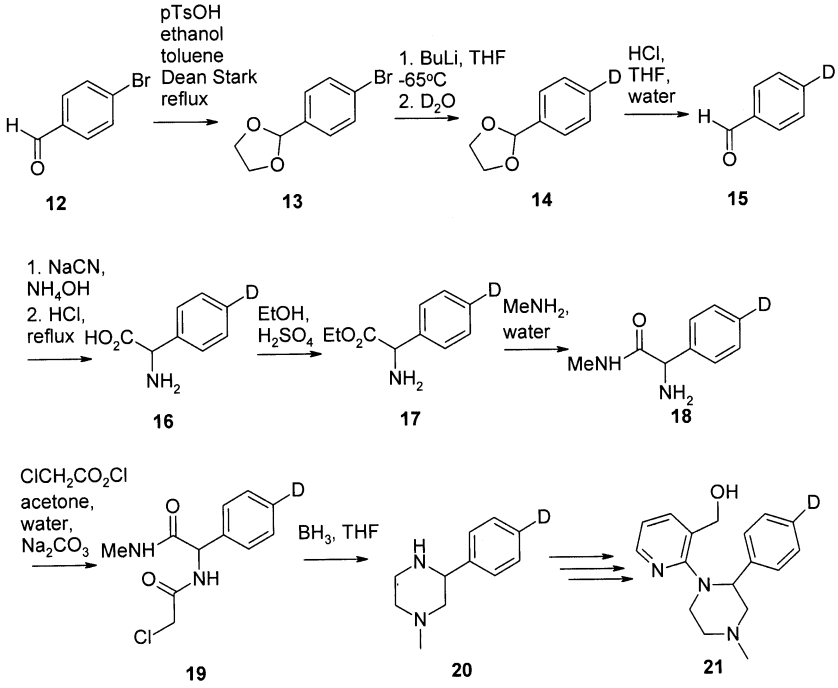
Figure 2. Structure of the side-product formed in the synthesis of (*S*)-mirtazapine.



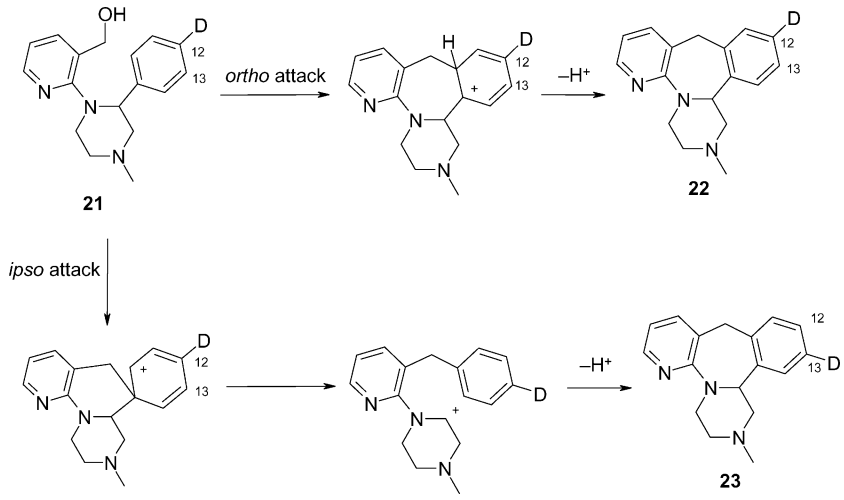
Scheme 3. Mechanism proposed for the racemization and side-product formation.

It was found that by using 2 wt.-equiv. of PPA for the ring-closing reaction, an asymmetric synthesis of (*S*)-mirtazapine could be achieved. By treating the alcohol or its oxalate salt with 2 wt.-equiv. of PPA at 130 °C, (*S*)-mirtazapine was obtained in excellent enantiopurity.[13] The impurities formed were effectively removed by crystallization of the maleate salt. The maleate salt was obtained in a yield between 60 and 70%.

In order to substantiate the mechanism shown in Scheme 3, the alcohol **21** was prepared with a deuterium label at the *para* position of the phenyl ring according to the synthesis shown in Scheme 4. To this end, *p*-bromobenzaldehyde (**12**) was protected as a diethyl acetal, lithiated at the position of the bromide and quenched in deuterium oxide. Hydrolysis of the ethyl acetal **14** furnished *p*-deuteriobenzaldehyde (**15**), which, by a Strecker synthesis, was converted into **16**. Compound **16** was converted into 1-methyl-3-(*p*-deuteriophenyl)piperazine (**20**) according to a procedure developed by Medichem.[14] From the deuteriated piperazine **20**, alcohol **21** was prepared by the route



Scheme 4. Synthesis of *p*-deuteriophenyl alcohol **21**.



Scheme 5. Anticipated position of the deuterium atom in mirtazapine after *ortho* and *ipso* attack.

described in Scheme 2. The NMR spectrum of **21** confirmed the presence of the deuterium atom exclusively at the *para* position of the phenyl substituent.

The deuteriated alcohol **21** was subjected to both racemizing and nonracemizing ring-closing conditions. Following the mechanism in Scheme 5, it can be deduced that after

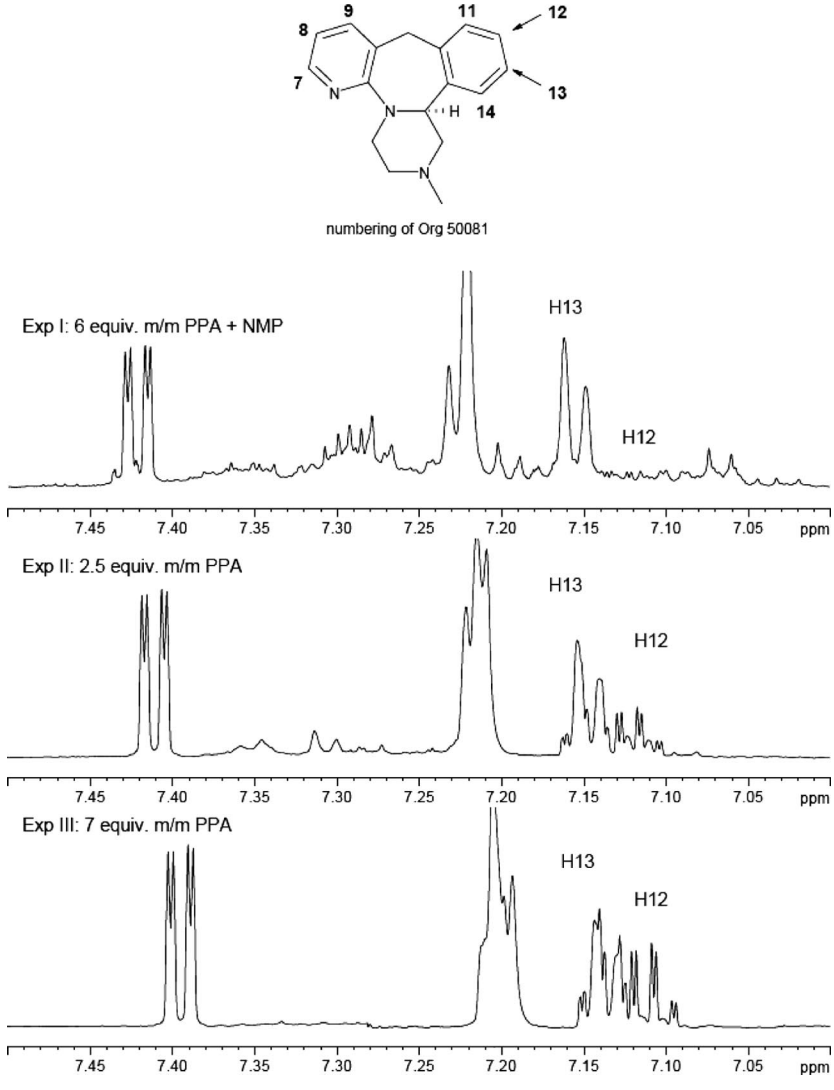


Figure 3. ^{1}H NMR spectra (600 MHz in acetone) obtained after the ring-closure step under different reaction conditions.

Table 3. Effect of different reaction conditions on the ring-closure step.

Exp.	Conditions	Yield (%)	Purity by GC (a/a%)
I	PPA (6 equiv., m/m) + NMP (28 vol.); 100 °C	86	96[a]
II	PPA (2.5 equiv., m/m); 100 °C	31	92[a]
III	PPA (7 equiv., m/m); 100 °C	51	99

[a] After silica gel chromatography.

ortho attack the deuterium atom will eventually be present in mirtazapine at the 12-position. On the other hand, if an *ipso* attack is involved as well, this would lead to mirtazapine with the deuterium atom at the 13-position. It was demonstrated that no scrambling of deuterium can take place under the reaction conditions using PPA. However, when the alcohol was subjected to reaction with deuteriated sulfuric acid scrambling of the hydrogen atoms of the phenyl ring was observed. Therefore, for the study with deuteriated alcohol **21**, only PPA was used.

The deuteriated alcohol was subjected to three different sets of reaction conditions, which resulted in no racemization (Experiment I), little racemization (Experiment II), and significant racemization (Experiment III). The NMR spectra of the products resulting from these experiments are shown in Figure 3[15] and the yields and purities of the products are compiled in Table 3. From Table 3 it can be seen that the reaction in diluted PPA (Experiment III) gave a relatively clean reaction product but that those with less equivalents of PPA and with PPA in combination with NMP required chromatographic purification. The purities of the products, as assessed by GC, were over 90% for all samples. From the NMR spectrum of the product formed under nonracemizing conditions, that is, Experiment I, it can be seen that the signal of 12-H is missing. Clearly, this position is completely blocked by the deuterium atom pointing to the formation of mirtazapine by normal *ortho* attack only. The experiment employing slightly racemizing conditions, Experiment II,[16] showed a signal arising from a hydrogen atom at the 12-position, whereas the signal of 13-H is smaller relative to the other signals. This indicates that part of the mirtazapine is formed by *ortho* attack, leaving the deuterium atom at the 12-position, and part of the mirtazapine is formed by *ipso* attack resulting in a shift of the deuterium atom to the 13-position. The NMR spectrum from Experiment III, in which significant racemization occurred, showed that the signal of 13-H had decreased further, whereas that of 12-H was higher. This is in line with the expectations in more diluted PPA without a coordinating solvent such as NMP, as in this medium racemization was more pronounced. In conclusion, the spectra in Figure 3 nicely support the mechanism proposed for racemization shown in Scheme 3.

Conclusions

An asymmetric synthesis of (*S*)-mirtazapine has successfully been derived from the synthesis of racemic mirtazapine starting from enantiomerically pure (*S*)-1-methyl-3-phenylpiperazine. Although this synthesis was initially hampered by racemization in the final step, this problem could be solved by using 2 wt.-equiv. of PPA instead of sulfuric acid for the electrophilic aromatic ring closure. A correlation between the extent of racemization and the amount of PPA used in this ring-closure reaction was observed. An *ipso*-attack mechanism was postulated to explain the racemization under more dilute conditions of PPA and the retention of *ee* concurrent with side-product formation at higher concentrations. This *ipso* attack is likely driven by the formation of a stabilized piperazine cation. The *ipso*-attack mechanism was supported by a mechanistic study using deuterium-labeled starting material for the final electrophilic ring-closing reaction.

Experimental Section

General Information: NMR spectra were recorded with a Bruker DPX 400 spectrometer. Chemical shifts are reported in parts per million (ppm). ^{1}H NMR chemical shifts are referenced to TMS as internal standard (abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, dd = double doublet, dt = double triplet, ax = axial, eq = equatorial). Mass spectra were recorded with a PE SCIEX API 165 spectrometer. Gas chromatography was performed with a HP6890N instrument obtained from Agilent with a Restek RTX-column (5 m × 0.25 mm inner diameter × 0.5 μm diameter film; injection temperature 250 °C with a FID detector; temperature program: starting at 60 °C, 30 °C min^{-1} up to 300 °C, held at 300 °C for 2 min.

The polyphosphoric acid was prepared by adding 1 weight equivalent of phosphorus pentoxide in portions to 85% phosphoric acid while maintaining the temperature below 140 °C. For example, 100 g P_2O_5 was added in portions to 100 g phosphoric acid.

(*S*)-1-Methyl-3-phenylpiperazine·(+)-Anicyphos Salt: (*R*,*S*)-1-Methyl-3-phenylpiperazine (**1**) (100 g, 567 mmol) and (+)-Anicyphos (154.5 g, 571 mmol) were dissolved in water (250 mL) by heating the mixture at reflux. After cooling down to room temperature a seed crystal was added. After 2 h, the white crystals formed were collected by filtration and dried in a vacuum oven at 40 °C for 21 h. This provided 121 g of the salt (48%) with an *ee* of 85.5%. The crystals were dissolved in water (119 mL) at reflux temperature. After cooling down crystallization started. After 1 h the crystals were collected by filtration and dried in a vacuum oven at 40 °C. The yield of the crystals of the (*S*)-1-methyl-3-phenylpiperazine·Anicyphos salt was 105.8 g (42%, *ee* 99.0%).

The *ee* was determined by HPLC analysis: Chiralcel OD 250 × 4.6 mm i.d. (Daicel), 5% isopropyl alcohol in hexane, flow rate 1.0 mL min^{-1}, UV detector, column temperature 40 °C, retention times 5.6 and 6.3 min.

(*S*)-1-Methyl-3-phenylpiperazine [(*S*)-2]: The (*S*)-1-methyl-3-phenylpiperazine·(+)Anicyphos salt (100 g) was suspended in dichloromethane (378 mL). A 25% ammonium hydroxide (63.2 mL) aqueous solution (315 mL) was added to this stirred suspension. The

layers were separated. The dichloromethane layer was washed three times with a saturated aqueous solution of sodium chloride. The dichloromethane layer was dried with magnesium sulfate and the solvents evaporated to dryness. This yielded 30.3 g (75%, *ee* 99.0%) of (*S*)-**2** as a colorless oil that crystallized upon standing. ^{1}H NMR ($CDCl_3$): δ = 1.90 (s, 1 H, NH), 2.0 (t, 1 H, CH_{ax}), 2.16 (dt, 1 H, CH_{ax}), 2.32 (s, 3 H, CH_3), 2.85 (m, 1 H, CH_{eq}), 2.89 (m, 1 H, CH_{eq}), 3.12 (dt, 1 H, CH_{ax}), 3.15 (m, 1 H, CH_{eq}), 3.88 (dd, 1 H, CH_{benzyl}), 7.23–7.41 (m, 5 H, Ar-H) ppm.

The *ee* was determined by HPLC analysis: Chiralcel OD 250 × 4.6 mm i.d., 10 μm (Daicel), 5% isopropyl alcohol in hexane, flow rate 1.0 mL min^{-1}, column temperature 40 °C, UV detector (210 nm), retention times 5.8 and 6.7 min.

2-[(2*S*)-4-Methyl-2-phenyl-1-piperazinyl]-3-pyridinecarbonitrile (3): A mixture of (*S*)-1-methyl-3-phenylpiperazine (*S*)-**2** (21.7 g, 123 mmol), 2-chloronicotinitrile (**1**) (21.7 g, 157 mmol), KF (21.7 g, 373 mmol), and DMF (65 mL) was heated at reflux for 23.5 h. The DMF was evaporated and ethyl acetate (45 mL) and water (64 mL) at 60 °C were added to the crude product. The mixture was refluxed for 10 min. The aqueous layer was separated from the organic layer and was extracted with ethyl acetate (45 mL). The collected ethyl acetate layers were evaporated to dryness. This furnished **3** (53.5 g, quantitative, *ee* 97.6%) as a brown oil that was directly used in the subsequent step. ^{1}H NMR ($CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 2.57 (m, 1 H, CH), 2.78 (m, 2 H), 2.95 (dd, 1 H, CH), 3.6 (m, 1 H, CH), 5.43 (t, 1 H, CH_{benzyl}), 6.79 (dd, 1 H, Ar-H), 7.18 (m, 1 H, Ar-H), 7.26 (m, 2 H, Ar-H), 7.37 (m, 1 H, Ar-H), 7.78 (dd, 1 H, Ar-H), 8.26 (dd, 1 H, Ar-H) ppm.

The *ee* was determined by HPLC analysis: Chiralcel OD-H 250 × 4.6 mm i.d., 10 μm (Daicel), 3% isopropyl alcohol in hexane + 0.1% diethylamine, flow rate 1.0 mL min^{-1}, column temperature 40 °C, UV detector (295 nm), retention times 6.6 and 7.7 min.

2-[(2*S*)-4-Methyl-2-phenyl-1-piperazinyl]-3-pyridinecarboxylic Acid (4): Nitrile (**3**) (53.5 g) was dissolved in methanol (86.8 mL) and the solution was heated to 50 °C. A 33% sodium hydroxide solution (127.4 mL) was added and the reaction mixture was refluxed for 3 days. The mixture was diluted with water (22 mL) and the methanol was evaporated. The thus formed oil was separated from the salty aqueous phase and dissolved in water (96 mL) by increasing the temperature to 80 °C. The pH was adjusted to 5.5 ± 0.5 by adding sulfuric acid and the solution was stirred for 15 min. Water was removed by co-evaporation with toluene (320 mL). The solution was filtered to remove the salts. The filtrate was evaporated to dryness and the crude product was co-evaporated twice with a mixture of methanol (87 mL) and water (2 mL). The residue was dissolved in acetone (109 mL) at 50 °C after which the solution was cooled to ambient temperature at which it was stirred overnight. The mixture was stirred for another hour at –10 °C after which the crystals of **4** were collected by filtration and dried in a vacuum oven. The yield of the crystals was 20.9 g (57%, *ee* > 99%). ^{1}H NMR ($CDCl_3$): δ = 2.43 (s, 3 H, CH_3), 2.61 (t, 2 H, CH_2), 3.12 (m, 3 H, CH_2, CH), 3.42 (dt, 1 H, CH), 4.79 (dd, 1 H, CH_{benzyl}), 7.11–7.28 (m, 4 H, Ar-H), 8.25 (dd, 1 H, Ar-H), 8.54 (dd, 1 H, Ar-H) ppm.

The *ee* was determined by HPLC analysis: Chiralcel OD-H 250 × 4.6 mm i.d., 10 μm (Daicel), 10% isopropyl alcohol in heptane, flow rate 1.0 mL min^{-1}, UV detector, column temperature 40 °C.

2-[(2*S*)-4-Methyl-2-phenyl-1-piperazinyl]-3-pyridinemethanol (5): Carboxylic acid **4** (15 g, 50 mmol) was dissolved in THF (80 mL) and $LiAlH_4$ (44 mL, 1 M in THF) was added. After stirring the reaction mixture for one night, the solution was cooled 10 °C and THF (4.6 mL), water (2.8 mL), and 33% sodium hydroxide solution (5.1 mL) were added. The mixture was heated at reflux for 30 min. The solution was cooled, magnesium sulfate was added, the salts were filtered, and the solvent was evaporated. The title compound was obtained as a colorless oil (15.9 g, 98%, purity by GC 99.7%, *ee* >99%). ^{1}H NMR ($CDCl_3$): δ = 2.31 (t, 1 H), 2.38 (s, 3 H, CH_3), 2.48 (dt, 1 H, CH), 2.98 (m, 2 H), 3.17 (m, 2 H), 4.61 (m, 1 H), 4.5 (dd, 1 H), 4.87 (d, 1 H, CH_{benzyl}), 5.30 (s, 1 H, OH), 6.88 (dd, 1 H, Ar-H), 7.08–7.19 (m, 2 H, Ar-H), 7.27–7.36 (m, 2 H, Ar-H), 8.16 (dd, 1 H, Ar-H) ppm.

The *ee* was determined by HPLC analysis: Chiralcel OJ 250 × 4.6 mm i.d., 10 μm (Daicel), 8% isopropyl alcohol in heptane + 0.1% diethylamine, flow rate 1.0 mL min^{-1}, column temperature 40 °C, UV detector (295 and 300 nm), retention times 7.0 and 12.5 min.

(14b*S*)-1,2,3,4,10,14b-Hexahydro-2-methylpyrazino[2,1-*a*]pyrido-[2,3-*c*][2]benzazepine [(*S*)-Mirtazapine]. Procedure A: A solution of **5** (7.02 g, 24.7 mmol) in *N*-methylpyrrolidinone (10 mL) was added to a mixture of polyphosphoric acid (41.8 g) and *N*-methylpyrolidine (10.5 mL). The reaction mixture was heated at 130 °C for 1 h. Water (152 mL), Dicalite (8.8 g), toluene (76 mL), and 33% sodium hydroxide solution (128 mL) were added to the reaction mixture. The aqueous layer was separated and extracted twice with toluene (76 mL). The combined toluene layers were washed three times with water (76 mL), dried with $MgSO_4$, and evaporated, to yield 4.63 g (*S*)-Mirtazapine (70%, *ee* 99%). ^{1}H NMR (MeOD): δ = 2.98 (s, 3 H, CH_3), 3.30 (dt, 1 H, CH), 2.86 (dt, 1 H, CH), 2.95 (dd, 1 H, CH), 3.42 (dd, 1 H, CH), 3.50 (dt, 1 H, CH), 3.69 (dt, 1 H, CH), 4.35 (dd, 1 H, CH), 4.52 (d, 1 H, CH_{benzyl}), 6.72 (dd, 1 H, Ar-H), 7.12–7.21 (m, 3 H, Ar-H), 7.25 (t, 1 H, Ar-H), 7.32 (dd, 1 H, Ar-H) ppm.

The *ee* was determined by HPLC analysis: Chiralcel OD-H 250 × 4.6 mm i.d. (Daicel), 10% isopropyl alcohol in heptane, flow rate 1.0 mL min^{-1}, column temperature 40 °C, UV detector, retention times 6.2 and 7.1 min.

Procedure B: A mixture of **5** (1.0 g, 3.53 mmol) and polyphosphoric acid (2 g) was stirred and heated at 130 °C for 18 h. The reaction mixture was diluted with water (6.5 mL) and the pH was brought to 8 by adding a 4 N sodium hydroxide solution. The water layer was extracted with ethyl acetate. The organic layer was washed with water, dried with magnesium sulfate, and the solvents evaporated. This provided the title compound (0.71 g, 76%, *ee* 98%).

Procedure C: A mixture of polyphosphoric acid (20 gram) and **5**·oxalic acid (13.2 g, 35.3 mmol) was stirred and heated at 130 °C for 18 h. Water (220 mL) was added followed by the addition of ethyl acetate (220 mL) and 33% sodium hydroxide solution (65 mL). The aqueous layer was separated and extracted twice with ethyl acetate (220 mL). The combined organic fractions were washed three times with water (220 mL) and the solvents evaporated. This gave 7.9 g (*S*)-mirtazapine (84%, *ee* 99.2%).

Isolation of the Side-Product 3-Benzyl-2-(2-methylaminoethyl)aminopyridine Trifluoroacetic Acid Salt (Figure 2): From the reaction mixture obtained by the above-described ring-closure reaction of **5** with 2 wt. equiv. of PPA, the title compound was isolated by preparative HPLC using a Gilson-semi*P*rep system with 25 wti pumps. An isocratic eluent with 90% acetonitrile and 10% water containing 0.1% formic acid was used. Flow-rate 20 mL min^{-1}. The column was obtained from Waters: Sunfire prep C18, OBP 10 μm, 19 × 150 mm. The injection volume was 750 μm. By using multiple injections 205 mg of 3-benzyl-2-[(2-methylaminoethyl)amino]pyridine was isolated.

MS: *m*/*z* = 242 [M + H]$^+$. MS/MS of *m*/*z* = 242: *m*/*z* = 211, 167, 133, 92. ^{13}C ATP ($CDCl_3$): δ = 33.4 (CH_3), 37.0 (CH_2), 39.6 (CH_2), 114.0 (CH), 122 (C), 127.3 (CH), 129.3 (4 CH), 137.7 (C), 139.0 (CH), 143.7 (CH), 155.79 (CH) ppm. ^{1}H NMR ($CDCl_3$): δ = 2.63 (s, 3 H, CH_3), 3.18 (s, 2 H, CH_2), 3.72 (s, 2 H, CH_2), 3.83 (s, 2 H, CH_2), 6.63 (m, 1 H, Ar-H), 7.16 (d, 2 H, Ar-H), 7.19 (d, 1 H, Ar-H), 7.25 (m, 1 H, Ar-H), 7.30 (m, 2 H, Ar-H), 7.95 (d, 1 H, Ar-H), 8.38 (s, 1 H, NH) ppm.

2-(4-Bromophenyl)-1,3-dioxolane (13): Ethylene glycol (1627 mmol, 91 mL, 101 g) and *p*-toluenesulfonic acid monohydrate (10.51 mmol, 2.0 g) were added to a solution of 4-bromobenzaldehyde (811 mmol, 150 g) in toluene (3.15 L). The mixture was heated at reflux (110 °C) and by using a Dean–Stark apparatus water was removed. After stirring overnight, the mixture was cooled to room temperature and extracted with water/ethyl acetate, washed with saturated aqueous NaCl, dried with $MgSO_4$, and concentrated in vacuo to yield the title compound in 181.5 g (792 mmol, 98%, purity according to GC 97% a/a) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 4.01–4.15 (m, 4 H,CH_2O), 5.76 (s, 1 H, CH) 7.35 (d, 2 H, ArH, *meta*), 7.52 (d, 2 H, ArH, *ortho*) ppm.

2-(4-Deuteriophenyl)-1,3-dioxalane (14): A 1.6 M solution of *n*-butyllithium (1200 mmol, 750 mL, 510 g) in hexane was slowly added to a solution of 2-(4-bromophenyl)-1,3-dioxolane (**13**) (792 mmol, 181.5 g) in THF (2.5 L) at –65 °C. After stirring for 30 min at –65 °C, deuterium oxide (5493 mmol, 100 mL, 110 g) was added carefully at a maximum temperature of –60 °C. The mixture was warmed to room temperature and was extracted with toluene (2 × 2 L). The combined organic layers were washed with water (2 × 1 L), dried with $MgSO_4$, and the solvents evaporated. This yields **14** in quantitative yield (purity according to GC 95% a/a) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 4.01–4.18 (m, 4 H,CH_2O), 5.82 (s, 1 H, CH), 7.38 (d, 2 H, ArH, *meta*), 7.50 (d, 2 H, ArH, *ortho*) ppm.

4-Deuteriobenzaldehyde (15): Water (100 mL) and *p*-toluenesulfonic acid monohydrate (10.51 mmol, 2 g) were added to a solution of 2-(4-deuteriophenyl)-1,3-dioxalane (**14**) (840 mmol, 127 g) in acetone (1 L). The reaction mixture was stirred overnight at room temperature. In order to achieve a complete conversion, four additional portions of *p*-toluenesulfonic acid monohydrate (10.51 mmol, 2 g) we added. The reaction mixture was diluted with toluene (2 L) and saturated sodium hydrogen carbonate (2 × 1 L). The toluene phase was separated and washed with saturated NaCl (2 × 1 L), dried with $MgSO_4$, and concentrated in vacuo to yield 67.5 g of **15** (75%, purity according to GC 95% a/a) as a liquid. ^{1}H NMR ($CDCl_3$): δ = 7.55 (d, 2 H, ArH, *meta*), 8.11 (d, 2 H, ArH, *ortho*), 10.2 (s, 1 H, CH) ppm.

rac*-4-Deuteriophenylglycine (16):** Ammonium chloride (654 mmol, 35 g) was added to a stirred solution of sodium cyanide (653 mmol, 32 g) in water (128 mL). This was followed by the addition of a solution of 4-deuteriobenzaldehyde (**15**) (627 mmol, 67.15 g) in MeOH (128 mL). During the addition the temperature rose from 10 to 30 °C. The reaction mixture was stirred for 2 h, water was added (300 mL), and the mixture was extracted twice with toluene (180 and 120 mL). The toluene phases were washed with water (2 × 100 mL) followed by extraction with a 5 N HCl solution (2 × 100 mL). The acidic extract was heated for 22 h at reflux. After cooling, the tarry black material was removed by filtration through a plug of cotton wool. The pH of the filtrate was adjusted to 6.2 by the addition of an ammonia solution (25 wt.-%) under cooling. The resulting precipitate was collected by filtration, washed with cold water (300 mL), and dried overnight to yield 63.4 g of **16** (66.5%) as off-white crystals. ^{1}H NMR (D_2O): δ = 4.23 (s, 1 H, $CHNH_2$), 7.24–7.32 (m, 4 H, ArH) ppm. ***Note: The ^{1}H NMR spectrum was recorded for the potassium salt.

Ethyl (*rac*)-Amino(4-deuteriophenyl)acetate (17): Concentrated sulfuric acid (1013 mmol, 54 mL, 99 g) was added to a solution of (*rac*)-4-deuteriophenylglycine (**16**) (417 mmol, 63.45 g) in ethanol (650 mL) over 30 min at room temperature. After stirring overnight, the reaction mixture was poured into a saturated Na_2CO_3 solution and extracted twice with ethyl acetate. The organic layer was separated and washed with a saturated NaCl solution, dried with $MgSO_4$, and concentrated in vacuo to yield 16.4 g of the title compound (22%) as a liquid. ^{1}H NMR ($CDCl_3$): δ = 1.22 (t, 3 H, CH_3), 3.69 (q, 2 H, CH_2), 4.55 [s, 1 H, $CH(CO)NH_2$], 7.31–7.43 (m, 4 H, ArH) ppm.

***rac*-2-Amino-2-(*p*-deuteriophenyl)-*N*-methylacetamide (18):** Ethyl (*rac*)-amino(*p*-deuteriophenyl)acetate (**17**) (139 mmol, 25 g) was dissolved in an ethanolic solution of methylamine (2196 mmol, 264 mL, 227 g). The reaction mixture was stirred overnight at 20 °C and concentrated in vacuo to yield 16.3 g of **18** (84%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 2.81 (s, 3 H, CH_3NH), 4.52 [s, 1 H, $CH(CO)NH_2$], 7.31–7.43 (m, 4 H, ArH) ppm.

***rac*-2-Chloroacetamido-2-(*p*-deuteriophenyl)-*N*-methylacetamide (19):** Sodium carbonate (59.2 mmol, 6.27 g) was added to a solution of (*rac*)-2-amino-2-(*p*-deuteriophenyl)-*N*-methylacetamide (**18**) (98 mmol, 16.2 g) in water (53 mL) and acetone (44 mL) at 20 °C. The mixture was cooled to 0 °C and stirred for 1.5 h. A solution of chloroacetyl chloride (104 mmol, 8.24 mL, 11.70 g) in acetone (30 mL) was slowly added. The resulting milky suspension was stirred at 0 °C for 1.5 h which was followed by the addition of Na_2CO_3 (1.25 g, 11.85 mmol) and a solution of chloroacetyl chloride (1.57 mL, 2.23 g, 19.7 mmol) in acetone (6 mL). After stirring for an additional 1.5 h, approximately 50 mL of solvent was removed at 44 °C under vacuum. The obtained thick suspension was cooled to 20 °C and filtered. The residue was washed with water (30 mL). The obtained material was dried overnight by passing nitrogen through the filter to yield 16.1 g of **19** (67.8%) as off-white crystals.

***rac*-3-(*p*-Deuteriophenyl)-1-methylpiperazine (20):** A solution of borane–tetrahydrofuran (300 mmol, 300 mL, 330 g) was added dropwise to a suspension of (*rac*)-2-chloroacetamido-2-(*p*-deuteriophenyl)-*N*-methylacetamide (**19**) (63.2 mmol, 15.28 g) in THF (160 mL). The reaction mixture was stirred overnight. Concentrated hydrochloric acid (336 mmol, 56 mL, 58.8 g) was added slowly at room temperature (a lot of hydrogen gas was formed). The mixture was distilled at reduced pressure to remove the THF. Ethyl acetate (150 mL) was added and the mixture was extracted with 2 N hydrochloric acid (3 × 100 mL). The pH of the combined acidic phases was adjusted to 12–13 by addition of an aqueous solution of sodium hydroxide (33%). The aqueous phase was extracted with ethyl acetate (3 × 100 mL). The combined organic phases were dried on $MgSO_4$, and concentrated in vacuo to give 7.7 g of **20** as a yellowish liquid (68.7%). ^{1}H NMR ($CDCl_3$): δ = 1.70 (s, 1 H, NH), 2.0 (t, 1 H, CH_{ax}), 2.16 (dt, 1 H, CH_{ax}), 2.33 (s, 3 H, CH_3), 2.85 (m, 1 H, CH_{eq}), 2.89 (m, 1 H, CH_{eq}), 3.02–3.16 (m, 2 H, CH_{ax}, CH_{eq}), 3.88 (dd, 1 H, CH_{benzyl}), 7.35 (m, 2 H, Ar-H), 7.38 (m, 2 H, Ar-H) ppm.

2-[(2*S*)-2-(4-Deuteriophenyl)-4-methyl-1-piperazinyl]-3-pyridinemethanol (21): The title compound was prepared from (*rac*)-3-(*p*-deuteriophenyl)-1-methylpiperazine (**20**) and 2-chloronicotinitrile according to the procedures described above for compounds **3**–**5**. ^{1}H NMR ($CDCl_3$): δ = 2.29 (t, 1 H), 2.38 (s, 3 H, CH_3), 2.50 (dt, 1 H, CH), 2.96 (m, 2 H), 3.20 (m, 2 H), 4.66 (m, 1 H, CH), 4.76 (d, 1 H, CH) 4.81 (d, 1 H, CH_{benzyl}), 6.99 (dd, 1 H, Ar-H), 7.08

(m, 2 H, Ar-H), 7.28 (m, 2 H, Ar-H), 7.77 (dd, 1 H, Ar-H), 8.03 (dd, 1 H, Ar-H) ppm.

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[10] Economically more viable syntheses for (*S*)-1-methyl-3-phenylpiperazine have also been identified, which will be reported in a separate paper.

[11] The polyphosphoric acid was prepared by adding 1 weight equivalent of phosphorus pentoxide in portions to phosphoric acid (85%) while maintaining the temperature below 140 °C. For example, 100 g P_2O_5 was added in portions to 100 g phosphoric acid.

[12] It should be noted that in reactions with PPA and DMF (entry 14 in Table 1) a side-product was observed in amounts of up to 26% relative to the product. This side-product was characterized by MS as having a MIM of 338, corresponding to a DMF adduct of a cationic intermediate. The side-product was not isolated or further characterized. However, it is a plausible hypothesis that the piperazine cation was attacked by DMF thereby preventing re-attack of the piperazine cation and thus avoiding formation of racemic mirtazapine.

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[15] The NMR spectra were recorded in deuteriated acetone in order to achieve sufficient resolution of the signals of the relevant protons 12 and 13.

[16] Because of the small scale of the reaction a little more than the intended 2.5 wt.-equiv. of PPA were used.

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