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Diastereoselective Hydrogenation of Pyrazine Derivatives: An Alternative Method of Preparing Piperazine-(2*S*)-Carboxylic Acid

Pavel Kukula and Roel Prins[1]

Laboratory for Technical Chemistry, Swiss Federal Institute of Technology (ETH), CH-8093 Zurich, Switzerland

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The diastereoselective hydrogenation of a chiral pyrazine derivative was used for the stereoselective preparation of piperazine-2-carboxylic acid, which is an important chiral building block. The study was focused on the diastereoselective hydrogenation with various noble metal catalysts (Pd, Pt, Rh, Ru) on different supports. It was found that intramolecular cyclization of the substrate takes place during the hydrogenation, forming an unsaturated diketopiperazine derivative. This intermediate was further hydrogenated to a mixture of saturated heterocyclic diastereomers. The influence of the reaction conditions (temperature, pressure of hydrogen, and type of solvent) on the diastereoselectivity was also studied. The highest diastereoselectivity (79%) was reached with 10% Pd/C and with water as solvent. The desired molecule of piperazine-2-carboxylic acid was finally obtained by acidic hydrolysis of the diastereomeric diketopiperazine adduct. © 2002 Elsevier Science (USA)

Key Words: **diastereoselective hydrogenation; pyrazine; proline auxiliary; optically active piperazine 2-carboxylic acid; nonproteinogenic amino acids.**

INTRODUCTION

The synthesis of optically pure substances is becoming increasingly important, and it is an essential part of many chemical procedures, especially in the production of pharmaceuticals, agrochemicals, and fragrance and flavor substances. Several different approaches are applied in the production of optically pure chiral substances (1), of which one is diastereoselective hydrogenation (2), in which a covalent bond between the prochiral substrate and the chiral molecule (auxiliary) is formed. Thus, the reactant itself represents the source of chirality and induces the formation of a new stereogenic center. Several reviews (2, 3) have already been published on this topic, and various applications have been described (4–8).

A large number of biologically active molecules contain chiral heterocyclic components, which can be prepared by stereoselective catalytic hydrogenation of the corresponding substituted aromatic compounds. Stereoselective synthesis of chiral *N*-heterocycles is of interest, because they are widely used in the life-science industry. During the last decade, nonproteinogenic amino acids and their derivatives received particular attention (9). One of the most important molecules is piperazine-(2*S*)-carboxylic acid because it is widely used as a chiral building block in a number of bioactive compounds, e.g., Merck's HIV protease inhibitor Indinavir (Crixivan) (10), an *N*-methyl-D-aspartate antagonist (11), various matrix-metalloproteinase inhibitors (12–14), and cardioprotective nucleoside transport blockers (15). Much work has, therefore, been devoted to the preparation of the enantiomerically pure piperazine-(2*S*)-carboxylic acid (16–20) and its derivatives (21–29) (mainly *N*-tert-butyl-2-piperazinecarboxamide—the Indinavir precursor). Current procedures involve the classical resolution of the racemate by fractional crystallization of diastereomeric salts (16, 23, 28, 29), the asymmetric synthesis and homogeneous catalytic hydrogenation with rhodium complexes (18, 24–27), and recently developed biocatalytic processes using the kinetic resolution of the piperazine-2-carboxamide racemate by amidases (17, 19, 20).

We report a new alternative for preparing piperazine-(2*S*)-carboxylic acid by diastereoselective hydrogenation of chirally modified pyrazine-2-carboxylic acid. Up to now, the hydrogenation of a substituted pyrazine ring has been investigated by several authors (30–37) using noble metal catalysts such as palladium, platinum, and rhodium supported on charcoal. In these cases, hydrogenation does not proceed easily because the metal catalyst is poisoned by secondary or tertiary nitrogen atoms in the product molecules. Therefore, more severe reaction conditions and longer reaction times are needed to complete the hydrogenation. The reactions are sometimes carried out in acidic media to prevent poisoning of the catalyst (33, 34). Palladium on charcoal is the most widely used catalyst for the hydrogenation of various pyrazine derivatives (30–32, 35–37). For example, if a large amount of catalyst is used, pyrazine-2-carboxylic acid can be hydrogenated to piperazine-2-carboxylic acid in the form of the sodium or potassium salt in aqueous medium already at 50°C and at atmospheric pressure of hydrogen (32). More stringent reaction conditions (85°C

[1] To whom correspondence should be addressed. Fax: 41-1-6321162. E-mail: prins@tech.chem.ethz.ch.

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and 2 MPa) were required during the hydrogenation of pyrazine-2-carboxylic acid amide (17).

The asymmetric hydrogenation of substituted pyrazine derivatives has been studied using homogeneous catalysts. The stereoselective hydrogenation of 1,4,5,6-tetrahydropyrazine-2-carboxylic acid derivatives, with protected nitrogens and a substituted carboxylic group, to the corresponding piperazine derivatives using chiral homogeneous rhodium complexes was described (24–27). The best results (96% yield, 99% *e.e.*) were obtained with the [(*R*)-BINAP(COD)Rh]TfO catalyst (26). The diastereoselective hydrogenation of pyrazine derivatives has not been attempted yet. Tungler and coworkers (38, 39) made the first attempts at hydrogenating aromatic *N*-containing heterocycles diastereoselectively. They carried out the hydrogenation of pyridine and pyrrole derivatives using noble metal catalysts (Pd, Rh, Ru, and Pt) and (*S*)-proline methylester as the chiral auxiliary. Some of the obtained diastereoselectivities were high, e.g., the hydrogenation of *N*-picolinoyl-(*S*)-proline methylester over Pd/C resulted in 79% *d.e.* and the hydrogenation of *N*-nicotinoyl-(*S*)-proline methylester in 94% *d.e.* Because of these promising results, we investigated the stereoselective formation of a new chiral center during the hydrogenation of pyrazine derivatives using the same chiral auxiliary.

This paper describes the diastereoselective hydrogenation of chirally modified pyrazine-2-carboxylic acid. The aim of the study was to prepare piperazine-(2*S*)-carboxylic acid stereoselectively. Pyrazine-2-carboxylic acid, which is commercially available in large amounts, was the starting material. The source of chiral information was introduced by means of a very common compound, the natural amino acid (*S*)-proline. The hydrogenation of pyrazine, modified by the proline auxiliary, was carried out using various heterogeneous noble metal catalysts; the influence of the reaction conditions on diastereoselectivity of hydrogenation was investigated. Finally, the procedure for the deprotection of the chiral auxiliary from the product molecule was tested.

EXPERIMENTAL

All the organic chemicals, with the exception of racemic piperazine-2-carboxylic acid (Aldrich), were purchased from Fluka. The organic solvents were used without further purification. The reaction course of hydrogenation was monitored by gas chromatography using an HP 5890 Series II Plus instrument equipped with an HP-1 capillary column. The intermediates and products of the reactions were analyzed by GC–MS (HP 5973 MSD). After the separation and isolation of the pure compounds, elementary analysis (automatic analyzer Perkin–Elmer CHN 240C) and ^{1}H and ^{13}C NMR spectroscopy (DPX 300 and AVANCE 500 from Bruker AG) were carried out for characterization. The crystal structure of the hydrogenation product was determined on a single-crystal four-circle X-ray diffractometer Syntex P21. The diastereoselectivity of hydrogenation was determined by GC and the diastereomeric excess (*d.e.*) was defined as: $d.e. = |([R,S\text{-diastereomer}] - [S,S\text{-diastereomer}])|/([R,S\text{-diastereomer}] + [S,S\text{-diastereomer}]) \times 100$. The enantioselectivity of hydrolysis and the optical purity of piperazine-2-carboxylic acid were determined by polarimetry (Perkin–Elmer 241) at 589 nm and by chiral HPLC (Agilent 1100 Series LC system, Macherey–Nagel column Nucleosil 120-3 C18, mobile phase: water : methanol (3 : 1) with 2 mM *N,N*-dimethyl-L-phenylalanine and 1 mM $CuSO_4 \cdot 5H_2O$).

Synthesis of the Pyrazine-2-(methyl-(S)-prolinecarboxamide) Substrate

Pyrazine-2-(methyl-(*S*)-prolinecarboxamide) was prepared by coupling the carboxylic group of pyrazine-2-carboxylic acid with the amino group of the methyl ester of (*S*)-proline hydrochloride according to the following procedure: Pyrazine-2-carboxylic acid (3.75 g, 30 mmol, 1 eq.) and 1-hydroxybenzotriazol, HOBT (4.85 g, 36 mmol, 1.2 eq.), were dissolved in 60 ml of chloroform and cooled to 0°C. The hydrochloride of the (*S*)-proline methylester (5 g, 30 mmol, 1 eq.), triethylamine (4.2 ml, 30 mmol, 1 eq.), and chloroform (40 ml) were added at regular intervals to the cooled, stirred solution. *N*,*N*′-Dicyclohexylcarbodiimide, DCC (6.2 g, 30 mmol, 1 eq.), was dissolved in 20 ml of chloroform and slowly added to the mixture. The cooling bath was removed and the mixture was stirred overnight. The formed dicyclohexylurea was filtered off, chloroform was evaporated, and ethylacetate was added to the residue. After the remaining dicyclohexylurea was filtered off, the organic phase was washed with a diluted HCl–water solution and an aqueous $NaHCO_3$ solution and dried over $MgSO_4$. The ethylacetate was evaporated to dryness *in vacuo* and 6.1 g of crystalline, slightly yellow pyrazine-2-(methyl-(*S*)-prolinecarboxamide) was obtained (yield 85%).

Diastereoselective Hydrogenation

The diastereoselective hydrogenation of pyrazine-2-(methyl-(*S*)-prolinecarboxamide) was carried out using various noble metal catalysts on different supports: 10 wt% Pd/C (Fluka, Cat. No. 75990), 5 wt% Pt/C (Fluka, Cat. No. 80982), 5 wt% Ru/C (Fluka, Cat. No. 84031), 5 wt% Rh/C (Fluka, Cat. No. 83711), 5 wt% Rh/Al_2O_3 (Fluka, Cat. No. 83720), and Rh black, 99 wt% (Johnson Matthey, Cat. No. 231-125-0). All catalysts were used directly as supplied. Experiments were carried out in a 60-ml stainless steel autoclave (Medimex AG) equipped with a sampling tube and magnetic gas-inducing impeller. In a typical experiment, 50 mg of pyrazine-2-(methyl-(*S*)-prolinecarboxamide) was dissolved in 30 ml of solvent and 10–40 mg of the catalyst

was added. The substrate-to-metal molar ratio was kept constant at S/M ~ 23. A rather large amount of catalyst with respect to substrate was required in order to obtain a reasonable reaction time because of the poisoning effect of the nitrogen atom in the substrate molecule. Nevertheless, all the reactions were conducted in the kinetic regime, because the reaction rate was proportional to the mass of the catalyst and not to the stirring speed. The slurry was then transferred to the autoclave and flushed three times with hydrogen. The autoclave was pressurized with hydrogen to 70 bar; and stirring (1000 rpm) and heating to the appropriate temperature were started. Samples of the reaction mixture were withdrawn during the reaction and analyzed by gas chromatography. After the hydrogenation was completed, the catalyst was filtered off, the solvent was evaporated, and the final product was dried under high vacuum. The product was characterized by GC–MS and NMR spectroscopy. The yields of the hydrogenation reactions were approximately 95%.

Hydrolysis of Hydrogenation Product

The product of total hydrogenation (diketopiperazine derivative, 100 mg, 0.48 mmol) was refluxed in 6 M HCl (10 ml) overnight. A white precipitate formed, was filtered off, washed with methanol, and dried under high vacuum. Organic elemental analysis and NMR spectroscopy proved that it consisted of the pure dihydrochloride of piperazine-(2)-carboxylic acid (93 mg, 96% yield). In order to check its optical purity the specific optical rotation was measured ($[\alpha]_D^{20} = 5.45^\circ$, $c = 1.2$, H_2O). This value corresponds to the data mentioned in the literature (15, 17, 28) for the pure dihydrochloride of (*S*)-piperazine-2-carboxylic acid, but it was not possible to estimate the exact enantiomeric ratio, since the published data differ slightly. Therefore, the acid was prepared from its hydrochloride, and the optical purity of the acid was measured by HPLC. A solution of piperazine-(2)-carboxylic acid dihydrochloride in 50 ml of water was passed over a cation exchange resin (Amberlite IR 120, 20 ml). After neutral washing of the exchanger with water, the resin was washed with diluted aqueous ammonia and water. The combined eluates, containing free piperazine-(2)-carboxylic acid (tested by TLC and detected with ninhydrin solution), were evaporated to dryness. The residual solid was recrystallized from a water–ethanol mixture, and the crystals were collected by filtration, and dried at 60°C. The yield was 57 mg (96%) of pure piperazine-(2)-carboxylic acid. The optical purity of the acid was measured by HPLC (see above).

RESULTS AND DISCUSSION

Preparation and Characterization of the Substrate

The reaction scheme of the stereoselective preparation of piperazine-(2*S*)-carboxylic acid (**1**) is shown in Fig. 1. The first step of the synthesis was the coupling of pyrazine-2-carboxylic acid (**2**) with the chiral auxiliary (*S*)-proline methylester (**3**) to form pyrazine-2-(methyl-(*S*)-prolinecarboxamide) (**4**). This reaction gave a very high yield of 85%. The ^{13}C and ^{1}H NMR measurements showed that at least two conformers of an amide (**4**) were present. All the signals of the carbon and hydrogen atoms in the ^{13}C and ^{1}H NMR spectra were double and the ratio of the

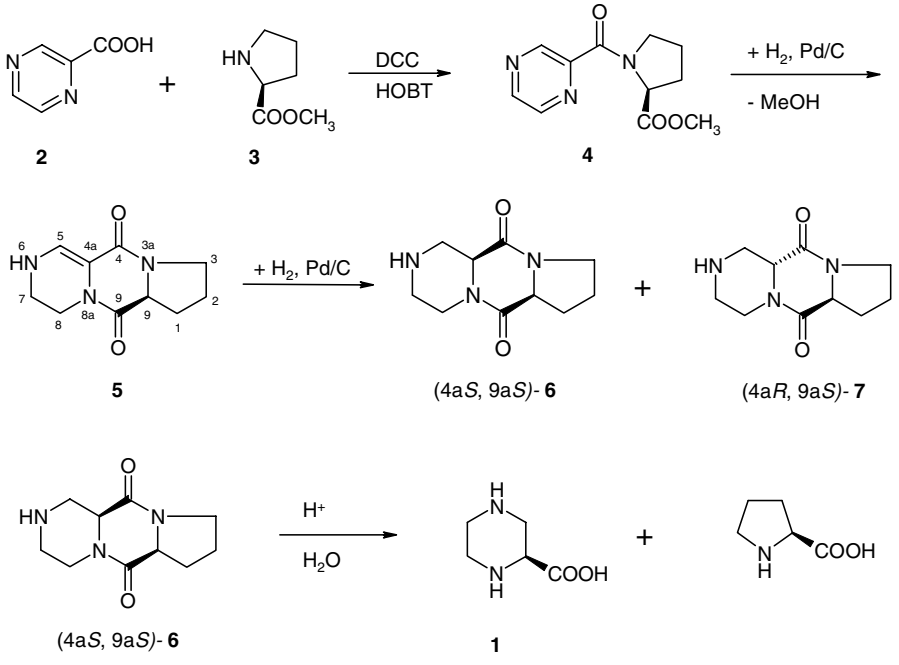

FIG. 1. Reaction scheme of the preparation of piperazine-(2*S*)-carboxylic acid.

signals for the same hydrogen and carbon atoms was approximately 50 : 50. For instance, the ^{1}H NMR spectrum of the substrate contains two doublets of doublets at 4.71 and 5.13 ppm, which were assigned to the proton on the chiral carbon atom of the proline auxiliary. The ratio of the signals was 49 : 51. In order to determine the structure of the conformers, molecular mechanics calculations were performed using the Hyperchem 5.0 software. Two structures with minimal energy were found. They differ in the orientation of the proline auxiliary, in particular the ester group, with respect to the aromatic pyrazine ring. In one of the conformers the ester group of the proline auxiliary is situated near the pyrazine ring, while in the other conformer it is facing away from the pyrazine ring. This is caused by a rotation of the amide bond by 180°. The interconversion between the conformers takes place at higher temperature, as was observed from ^{1}H NMR spectra measured in DMSO between 30 and 130°C. The signals of the protons on the pyrazine ring and the signals of the proton at the chiral carbon atom started to merge at 100°C and at 130°C there were only single signals for these protons in the spectrum.

Diastereoselective Hydrogenation

The diastereoselective hydrogenation of pyrazine-2-(methyl-(*S*)-prolinecarboxamide) (**4**) was initially studied using the palladium catalyst and methanol as the solvent. During these preliminary experiments it was found that the reaction proceeds via the partly hydrogenated intermediate (**5**) to a mixture of saturated diastereomers (**6** and **7**) (Fig. 1). The intermediate was probably formed by the intramolecular *N*-acylation of the partly hydrogenated substrate. At the same time, a methanol molecule was formed as the product of splitting the ester group of the proline auxiliary. The intramolecular cyclization was probably very fast, since we did not observe the formation of a partly hydrogenated substrate or of a noncyclic saturated product. In order to characterize the intermediate, the reaction was stopped at close to maximum concentration, and the intermediate was separated from the reaction mixture by column chromatography (3 MeOH : 1 $CHCl_3$). The structure of the intermediate was confirmed by ^{13}C and ^{1}H NMR measurements. As can be seen from the ^{13}C NMR data (see Appendix), there were two tertiary and three quaternary carbon atoms. Two of the quaternary carbons belong to the carbonyl groups, while the third must belong to the unsaturated carbon atom C-4a at the diketopiperazine ring, since the signal for this carbon atom was not present in the DEPT spectrum. Moreover, the presence of only two tertiary carbons and their chemical shifts indicate the position of a double bond in the tetrahydropyrazine ring of the intermediate (**5**) (Fig. 1).

The main products of the total hydrogenation were two diastereomers: (4a*S*, 9a*S*)- and (4a*R*, 9a*S*)-octahydro-3a,6,8a-triaza-cyclopenta[b]naphthalene-4,9-dione (**6** and **7**). The ratio of the diastereomers obtained by GC was approximately 8 : 2. The ^{13}C and ^{1}H NMR spectra also showed two sets of signals at roughly the same ratio. The diastereomers were purified by crystallization from toluene; one of them crystallizes preferentially from the toluene solution. Thus, the first of the formed crystals, which contained only one diastereomer, was collected and subjected to a structural analysis by NMR and X-ray diffraction (see Appendix). Figure 2 shows the ORTEP drawing of the crystal structure of this diastereomer obtained by XRD. It is apparent that the hydrogens at both chiral centers (C-4a and C-9a) are oriented in the same direction, toward the plane of projection, and that the configuration on both chiral centers is (4a*S*, 9a*S*). ^{1}H and ^{13}C NMR experiments confirmed the presence of only one diastereomer, but additional ^{1}H–^{1}H COSY, NOESY, and H,C–COSY experiments had to be carried out in order to resolve the spectra and prove the structure of the favored diastereomer. The NOESY experiment should confirm the configuration on the C-4a carbon by the expected interaction between two protons on the chiral carbon atoms C-4a and C-9a. The distance between these protons, as obtained from the crystal structure, was only approximately 0.3 nm. Nevertheless, no NOE interaction for these two protons was found. The resolved NMR spectra with assigned H and C atoms are given in the Appendix.

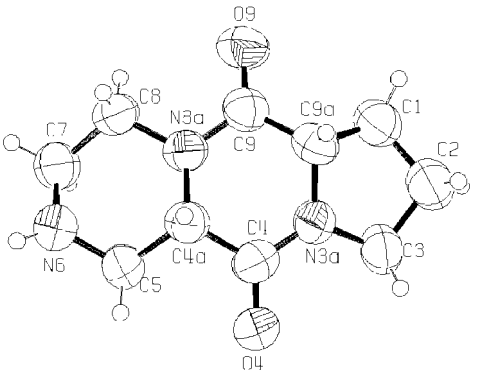

FIG. 2. ORTEP drawing of the hydrogenation product (**6**).

After the preliminary experiments with the palladium catalyst, the effect of other noble metal catalysts (Pt, Rh, and Ru) supported on different supports was studied. The experiments were carried out under the same reaction conditions, and the results are summarized in Table 1. The activities of the catalysts are reported as integral turnover frequency at 50% conversion of the substrate. Because the reaction of the substrate is complex and includes hydrogenation as well as ring formation we also present the reaction time, defined as time at which 100% conversion of the intermediate (**5**) was reached. The main by-products found in the reaction mixture were identified by GC–MS as two saturated diastereomers with the same structure as the product but methylated at the secondary nitrogen

TABLE 1

Comparison of Different Noble Metal Catalysts during the Hydrogenation of Pyrazine-2-(methyl-(*S*)-prolinecarboxamide) in Methanol at 80°C and 8 MPa

Catalyst	TOF at 50% conv. (h^{-1})	Reaction time (h)	Maximum content of intermediate (%)	Content of by-products (%)	*d.e.* (%)
Pd/C	104.1	1.3	75	3	67
Rh/C	62.7	2.2	31	<1	47
Pt/C	46.8	4.5	17	8	24
Ru/C	12.9	14.8	44	4	44
Rh/Al_2O_3	33.9	5.5	36	<1	46
Rh-black	7.3	3.0	16	9	43

atom (N-6). Their ratio corresponds roughly to the ratio of the diastereomers (**6** and **7**) and thus they were probably formed by the reaction of the products with the methanol solvent (experiments with other solvents see below). The most active catalyst was 10% Pd/C, with which the highest content of intermediates as well as the highest diastereoselectivity were reached. The activity, the maximum concentration of the intermediate, and the diastereoselectivity were considerably lower with the other catalysts. The lowest diastereoselectivity as well as the lowest concentration of the intermediate were obtained with the platinum catalyst. The ruthenium on active carbon catalyst was the least active catalyst. Nevertheless, the diastereoselectivity obtained with ruthenium was the same as with rhodium on carbon. The influence of the support was tested with the rhodium catalyst; it was found that it has a minimum effect on diastereoselectivity, and a considerable effect on TOF. The lower the total surface area of the catalyst, the lower the TOF of the reaction. The type of catalyst support probably affects both hydrogenation and intramolecular cyclization.

The results show that there is a relationship between the final diastereoselectivity and the maximum concentration of the intermediate. The higher the concentration of the intermediate during the reaction, the higher the diastereoselectivity. This phenomenon is not unexpected, because the structure of the cyclic intermediate is much more rigid than that of the substrate molecule. Therefore, the adsorption of the intermediate from one of its two diastereotopic faces on the catalyst is preferred and, thus, the formation of only one diastereomer is favored.

The course of the hydrogenation reaction and the development of diastereoselectivity during the reaction over the palladium catalyst are shown in Fig. 3. The diastereoselectivity first increases with the conversion of the substrate and then remains constant. A possible explanation is that this is caused by the total hydrogenation of the substrate followed by fast cyclization of the saturated product, which proceeds with a lower *d.e.* and can occur at the beginning of the reaction. A more probable explanation is that the catalyst is modified by the chiral reaction intermediates or products. These molecules are strongly adsorbed on the surface with their nitrogen atoms and can thus influence the mode of adsorption of the substrate and the diastereoselectivity of the hydrogenation.

A lower temperature usually favors higher diastereoselectivity. Therefore, the influence of the reaction temperature on diastereoselectivity was studied at temperatures between 50 and 85°C with platinum and rhodium catalysts. It was found that the reaction temperature considerably affected the reaction rate but had no significant influence on diastereoselectivity. This is probably due to the high conformational stability of the intermediate in the studied temperature region. A similar effect was observed for hydrogen pressure. In the region of 5–10 MPa, no significant changes in diastereoselectivity were observed, and the higher hydrogen pressure resulted only in a higher reaction rate.

Solvents are also known to play a role in determining the stereoselectivity in hydrogenation reactions. Therefore, the influence of solvents other than methanol on the hydrogenation of the substrate was investigated. The results of experiments carried out with the Pd/C catalyst and with solvents of different polarity are shown in Table 2. The type of solvent mostly affected the TOF of the reaction and the formation of the intermediate. There were no drastic differences in diastereoselectivity with different solvents. The reaction rate was lower for solvents with lower polarities. This may be caused not only by the lower hydrogenation activity but also by the lower rate of intramolecular cyclization, which is influenced by the reaction medium. Protic solvents such as water facilitate the intramolecular cyclization of the substrate by the protonation of the carbonyl group of the proline auxiliary. Therefore, the maximum content of the intermediate was higher with solvents of higher polarity. The higher value obtained with

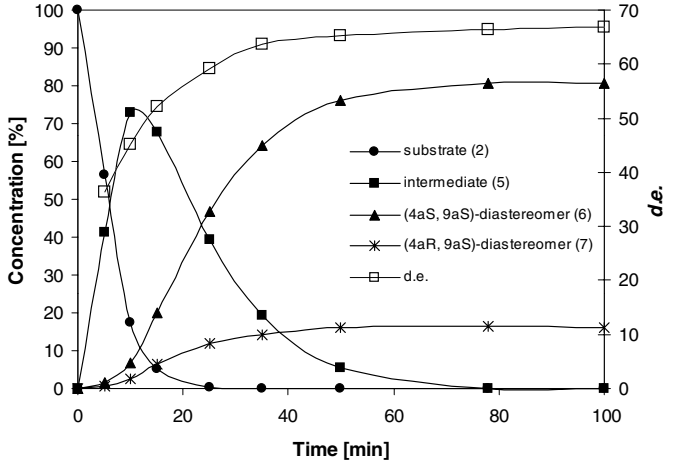

FIG. 3. Reaction course of pyrazine-2-(methyl-(*S*)-prolinecarboxamide) hydrogenation. Catalyst, 10% Pd/C; solvent methanol, $T = 80°C$, $p(H_2) = 8$ MPa, *d.e.* = 67%.

TABLE 2

Effect of the Solvent on the Hydrogenation of Pyrazine-2-(methyl-(*S*)-prolinecarboxamide) over a Pd/C Catalyst at 80°C and 8 MPa

Solvent	TOF at 50% conv. (h^{-1})	Reaction time (h)	Maximum content of intermediate (%)	Content of by-products (%)	*d.e.* (%)
Water	264.4	0.8	76	—	79
MeOH	104.1	1.3	75	3	67
EtOH	98.6	3.7	73	5	71
2-PrOH	46.0	5.4	62	—	64
t-BuOH	23.9	11.1	54	—	67
DMF	31.8	9.6	69	—	65
THF	25.4	6.8	38	9	68
EtOAc	17.0	7.8	37	—	74

DMF may be attributed to the fact that it can stabilize the protonated transition state of cyclization. The highest reaction rate as well as the highest diastereoselectivity were obtained with water. The main advantages of water are its high polarity, proton transfer ability, and good solubility with all reaction components.

Some by-products were formed during the reaction with methanol, ethanol, and tetrahydrofuran. As mentioned above, the by-products of the reaction with methanol were *N*-methylated diastereomeric products. GC–MS showed that the by-products of the reaction with ethanol were also saturated final diastereomers with *N*-ethylated secondary nitrogen atoms (N-6). No *N*-methylated by-products were observed in the reaction with ethanol. This supports the assumption that the by-products are formed by the reaction with the solvent and not with the methanol cleaved from the substrate. The by-products formed during the reaction with THF were not identified.

Deprotection of the Chiral Auxiliary and Preparation of Piperazine-2-carboxylic Acid

The mixture of both diastereomers 77 (**6**) : 23 (**7**) obtained after hydrogenation was subjected to acidic hydrolysis with aqueous hydrochloric acid to produce the hydrochlorides of piperazine-(2)-carboxylic acid and (*S*)-proline (Fig. 1). The piperazine-(2)-carboxylic acid dihydrochloride formed a precipitate in the reaction mixture and could thus be easily separated from the (*S*)-proline hydrochloride, which remained dissolved in the acidic aqueous solution. This advantageous separation of the two amino acids was very sensitive to changes in the concentration and pH of the solution. Since the determination of the optical purity of the dihydrochloride of piperazine-(2)-carboxylic acid by polarimetry was not very accurate (see experimental part), the free base of piperazine-2-carboxylic acid was prepared, and its optical purity was determined by the chiral separation (HPLC) of the enantiomers. The ratio (77 : 23) of the enantiomers of piperazine-2-carboxylic acid did not change. This proved that racemization of the hydrogenation products did not occur during the acidic hydrolysis. The yield of the hydrolysis and subsequent transformation of the dihydrochloride to the free base was approximately 92%.

CONCLUSION

A new method for the stereoselective preparation of piperazine-(2*S*)-carboxylic acid was discovered. It consists of three simple steps: coupling of the precursor with a chiral auxiliary, heterogeneous hydrogenation, and acidic hydrolysis. All the steps were completed with a yield higher than 85%. The diastereoselectivity obtained in the hydrogenation of the substrate over a palladium catalyst was considerably higher than over Rh, Ru, and Pt catalysts. The better performance of palladium is attributed to the formation of a larger amount of intermediate, which has a greater molecular rigidity and thus facilitates the differentiation of the two diastereotopic faces on the metal surface of the catalyst. The separation of the two diastereomers from the hydrogenation product by crystallization allows an increase in the *d.e.* value to almost 100% diastereoselectivity. Since the hydrolysis of the hydrogenation product proceeds without racemization, the preparation of enantiomerically pure piperazine-(2*S*)-carboxylic acid is attainable.

The described procedure for the stereoselective preparation of piperazine-2-carboxylic acid has the following advantages: inexpensive starting materials, heterogeneous hydrogenation (easy separation of the catalyst), the possible separation of the diastereomeric hydrogenation products, and, last but not least, the recycling of the chiral auxiliary (*S*)-proline.

APPENDIX

NMR, XRD, GC–MS, and elemental analysis data of the reaction components.

*Pyrazine-2-(methyl-(S)-prolinecarboxamide) (**4**)*

^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ (ppm) 1.95–2.37 (m, 4H, 2 × CH_2), 3.65 and 3.78 (s, 3H, OCH_3), 3.80–4.03 (m, 2H, CH_2), 4.71 (dd, $J = 4.5$ Hz, 8.7 Hz, 0.5H) and 5.13 (dd, $J = 3.1$ Hz, 8.7 Hz, 0.5H), 8.44 and 8.57 (dd, $J = 1.5$ Hz, 2.5 Hz, 1H, CH=N), 8.63 and 8.66 (d, $J = 2.5$ Hz, 1H, CH=N), 9.19 and 9.29 (d, $J = 1.5$ Hz, 1H, CH=N). ^{13}C NMR (125 MHz, $CDCl_3$, 25°C): δ (ppm) 21.9 and 25.5 (CH_2), 28.8 and 31.9 (CH_2), 48.4 and 49.7 (CH_2N), 52.2 and 52.4 (OCH_3), 60.3 and 61.4 (CH), 141.5 and 142.3 (CH=N), 145.7 and 145.8 (CH=N), 146.3 and 146.6 (CH=N), 147.8 and 148.4 (CH=N), 163.8 and 164.2 (CON), 172.4 and 173.1 (COO). ^{13}C DEPT NMR: δ (ppm) 21.9, 25.5, 28.8, 31.9, 48.4, 49.7 (all CH_2); 52.2, 52.4, 60.3, 61.4, 141.5, 142.3, 145.7, 145.8, 146.3, 146.6, 147.8, 148.4 (CH & CH_3). MS (EI, 70 eV): 235 (M^+, 12), 176 (95), 128 (100), 106 (86), 79 (90), 68 (30), 52

(42), 41 (26), 28 (14). Anal. Calc. for $C_{11}H_{13}N_3O_3$ (235.24): C 56.16, H 5.57, N 17.86; found: C 55.87, H 5.65, N 17.76.

Piperazine-(2)-carboxylic Acid Dihydrochloride

^{1}H NMR (300 MHz, D_2O, 25°C): δ (ppm) 2.75–2.87 (m, 2H), 2.93 (dd, 1H), 3.05 (dd, 1H), 3.17 (dt, 1H), 3.32 (dd, 1H), 3.48 (dd, 1H, C*H). ^{13}C NMR (75 MHz, D_2O, 25°C): δ (ppm) 41.65, 41.90, 44.98 (CH_2), 56.94 (C*H), and 173.25 (CO). M.p. 247–253°C (with decomposition). Anal. Calc. for $C_5H_{10}N_2O_2 \cdot 2HCl$ (203.07): C 29.57, H 5.96, N 13.80; found: C 29.67, H 5.85, N 13.87.

*Piperazine-(2)-carboxylic Acid (**1**)*

M.p. 270–273°C (with decomposition). Anal. Calc. for $C_5H_{10}N_2O_2$ (130.15): C 46.14, H 7.74, N 21.52; found: C 46.09, H 7.64, N 21.56.

*1,2,3,7,8,9a-Hexahydro-6H-3a,6,8a-triaza-cyclopenta[b]naphthalene-4,9-dione (**5**)*

^{1}H NMR (300 MHz, $CDCl_3$, 25°): δ (ppm) 1.86–2.11 (m, 3H), 2.34–2.45 (m, 1H), 3.05 (ddd, $J = 3.4$ Hz, 10.2 Hz, 13.0 Hz, 1H), 3.30 (dt, 1H), 3.45–3.74 (m, 3H), 4.10 (dd, $J = 6.3$ Hz, 9.6 Hz, 1H), 4.57 (d, $J = 12.6$ Hz, 2H), 6.01 (d, $J = 5.9$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ (ppm) 22.1, 29.0, 37.6, 40.2, 44.7 (d, CH_2), 59.0 (t, C*H), 105.9 (q, C–N), 125.6 (t, CH–N), 159.6, and 162.7 (q, C=O). MS (EI, 70 eV): 207 (M^+, 90), 178 (23), 151 (84), 110 (16), 82 (47), 70 (100), 54 (37), 41 (41), 28 (68). Anal. Calc. for $C_{10}H_{13}N_3O_2$ (207.23): C 57.96, H 6.32, N 20.28; found: C 57.79, H 6.43, N 20.16.

*(4aS, 9aS)-Octahydro-3a,6,8a-triaza-cyclopenta[b]naphthalene-4,9-dione (**6**)*

^{1}H NMR (500 MHz, C_6D_6, 25°C): δ (ppm) 0.76 (s, H-6), 0.94–1.04 (m, H-2-a), 1.09–1.16 (m, H-2-b), 1.53–1.61 (m, H-1-a), 1.97–2.02 (m, H-1-b), 2.04–2.10 (m, H-8-a), 2.31–2.40 (m, 2H, H-7-a, H-8-b), 2.46 (dd, $J_{\text{H-5-a,H-4a}} = 10.8$ Hz, $J_{\text{H-5-a,H-5-b}} = 12.5$ Hz, H-5-a), 3.01–3.05 (m, H-3-a), 3.23 (dd, $J = 6.3$ Hz, $J = 10.5$ Hz, H-9a), 3.32–3.38 (m, H-3-b), 3.47 (dd, $J_{\text{H-4a,H-5-b}} = 4.0$ Hz, $J_{\text{H-4a,H-5-a}} = 10.8$ Hz, H-4a), 3.58 (ddd, $J_{\text{H-5-b,H-7-b}} = 1.5$ Hz, $J_{\text{H-4a,H-5-b}} = 4.0$ Hz, $J_{\text{H-5-b,H-5-a}} = 12.5$ Hz, H-5-b), 4.34–4.38 (m, $J_{\text{H-7-b,H-5-b}} = 1.5$ Hz, H-7-b). ^{13}C NMR (125 MHz, $CDCl_3$, 25°C): δ (ppm) 21.78 (t, C-2), 29.79 (t, C-1), 42.14 (t, C-3), 44.83 (t, C-8), 45.23 (t, C-7), 48.93 (t, C-5), 57.63 (d, C-9a), 58.49 (d, C-4a), 163.10 (s, C-9), 167.17 (s, C-4). MS (EI, 70 eV): 209 (M^+, 85), 192 (15), 154 (32), 139 (60), 124 (12), 112 (12), 86 (68), 70 (100), 56 (49), 55 (54), 42 (43), 41 (47), 28 (49). Anal. Calc. for $C_{10}H_{15}N_3O_2$ (209.25): C 57.40, H 7.23, N 20.08; found: C 57.19, H 7.24, N 19.93. Crystal data and structure refinement, and bond length and valence angles of (**6**), are summarized in Tables 3 and 4.

TABLE 3

Crystal Data and Structure Refinement of (4a*S*, 9a*S*)-Octahydro-3a,6,8a-triaza-cyclopenta[b]naphthalene-4,9-dione (6)

Empirical formula	$C_{10}H_{15}N_3O_2 \cdot H_2O$
Formula weight	227.27
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	$a = 8.77(6)$ Å, alpha = 90 deg. $b = 6.82(4)$ Å, beta = 94.8(5) deg. $c = 9.07(7)$ Å, gamma = 90 deg.
Volume	540(6) Å^3
Z	2
Density (calculated)	1.397 Mg/m^3
Absorption coefficient	0.104 mm^{-1}
$F(000)$	244
Crystal size	0.1 × 0.1 × 0.1 mm
Theta range for data collection	2.25–20.53 deg.
Index ranges	$-8 \le h \le 8$, $-6 \le k \le 6$, $-8 \le l \le 8$
Reflections collected	2153
Independent reflections	1080 [R(int) = 0.0293]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1080/3/152
Goodness-of-fit on F^2	0.945
Final R indices [$I > 2$sigma(I)]	$R1 = 0.0620$, $wR2 = 0.1465$
R indices (all data)	$R1 = 0.0677$, $wR2 = 0.1516$
Extinction coefficient	0.35(4)
Largest diff. peak and hole	0.221 and −0.213 e.Å^{-3}

TABLE 4

Bond Lengths (Å) and Angles (Deg) of (4a*S*, 9a*S*)-Octahydro-3a,6,8a-triaza-cyclopenta[b]naphthalene-4,9-dione (6)

O(9)–C(9)	1.226(9)	N(3a)–C(9a)	1.456(9)
N(8a)–C(9)	1.364(9)	C(9a)–C(9)	1.482(11)
N(8a)–C(8)	1.461(11)	C(9a)–C(1)	1.496(11)
N(8a)–C(4a)	1.485(10)	C(5)–N(6)	1.440(11)
C(4a)–C(4)	1.492(11)	N(6)–C(7)	1.437(11)
C(4a)–C(5)	1.512(11)	C(7)–C(8)	1.525(12)
C(4)–O(4)	1.246(9)	C(3)–C(2)	1.521(12)
C(4)–N(3a)	1.331(9)	C(2)–C(1)	1.528(13)
N(3a)–C(3)	1.457(11)		
C(9)–N(8a)–C(8)	118.1(5)	N(3a)–C(9a)–C(1)	102.5(6)
C(9)–N(8a)–C(4a)	120.3(5)	C(9)–C(9a)–C(1)	116.3(6)
C(8)–N(8a)–C(4a)	116.5(6)	O(9)–C(9)–N(8a)	121.7(6)
N(8a)–C(4a)–C(4)	111.2(6)	O(9)–C(9)–C(9a)	121.8(6)
N(8a)–C(4a)–C(5)	109.7(5)	N(8a)–C(9)–C(9a)	116.4(5)
C(4)–C(4a)–C(5)	109.4(5)	N(6)–C(5)–C(4a)	111.0(4)
O(4)–C(4)–N(3a)	122.0(6)	C(7)–N(6)–C(5)	109.8(6)
O(4)–C(4)–C(4a)	120.9(6)	N(6)–C(7)–C(8)	108.6(5)
N(3a)–C(4)–C(4a)	117.1(6)	N(8a)–C(8)–C(7)	111.7(4)
C(4)–N(3a)–C(3)	125.3(5)	N(3a)–C(3)–C(2)	103.1(5)
C(4)–N(3a)–C(9a)	121.9(6)	C(3)–C(2)–C(1)	103.0(5)
C(3)–N(3a)–C(9a)	112.8(5)	C(9a)–C(1)–C(2)	103.7(6)
N(3a)–C(9a)–C(9)	113.2(6)		

*(4aR, 9aS)-Octahydro-3a,6,8a-triaza-cyclopenta[b]naphthalene-4,9-dione (**7**)*

The ^{13}C NMR spectrum of the (4a*R*, 9a*S*)-diastereomer was obtained from a sample in which the concentration was about 20%. In comparison with the (4a*S*, 9a*S*)-diastereomer, all the signals were slightly shifted. ^{13}C NMR (125 MHz, $CDCl_3$, 25°C): δ (ppm) 21.68 (t, C-2), 29.86 (t, C-1), 43.10 (t, C-3), 45.06 (t, C-8), 45.31 (t, C-7), 49.40 (t, C-5), 58.83 (d, C-9a), 62.58 (d, C-4a), 162.51 (s, C-9), 164.16 (s, C-4).

CCDC 181774 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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REFERENCES

1. Sheldon, R. A., "Chirotechnology." Decker, New York, 1993.
2. Besson, M., and Pinel, C., *Topics Catal.* **5**, 25 (1998).
3. Tungler, A., and Fodor, K., *Catal. Today* **37**, 191 (1997).
4. Besson, M., Gallezot, P., Neto, S., and Pinel, C., *Tetrahedron Asymmetry* **11**, 1809 (2000).
5. Ranade, V. S., Consiglio, G., and Prins, R., *Catal. Lett.* **58**, 71 (1999).
6. Gertosio, V., Santini, C. C., Basset, J. M., Bayard, F., Buendia, J., and Vivat, M., *J. Mol. Catal.* **142**, 141 (1999).
7. Tungler, A., Fürcht, A., Karancsi, Zs. P., Toth, G., Mathé, T., Hegedus, L., and Sandi, A., *J. Mol. Catal.* **139**, 239 (1999).
8. Mateus, C. R., Almeida, W. P., and Coelho, F., *Tetrahedron Lett.* **41**, 2533 (2000).
9. Petersen, M., and Sauter, M., *Chimia* **53**, 608 (1999).
10. Askin, D., Eng, K. K., Rossen, K., Purick, R. M., Wells, R. P., Volante, R. P., and Reider, P. J., *Tetrahedron Lett.* **35**, 673 (1994).
11. Bigge, C. F., Johnson, G., Ortwine, D. F., Drummond, J. T., Retz, D. M., Brahce, L. J., Marcoux, F. W., and Probert, A. W., *J. Med. Chem.* **35**, 1371 (1992).
12. Neya, M., Yamazaki, H., Kayakiri, N., Satto, K., and Oku, T., WO Patent 98/27069 (1998).
13. De, B., Natchus, M. G., Pikul, S., Almstead, N. G., Matthews, R. S., Taiwo, Y. O., and Cheng, M., WO Patent 98/08825 (1998).
14. Cheng, M., De, B., Pikul, S., Almstead, N. G., Natchus, M. G., Anastasio, M. V., McPhail, S. J., Snider, C. E., Taiwo, Y. O., Chen, L., Dunaway, C. M., Gu, F., Dowty, M. E., Mieling, G. E., Janusz, M. J., and Wang-Weigand, S., *J. Med. Chem.* **43**, 369 (2000).
15. Bruce, M. A., St. Laurent, D. R., Poindexter, G. S., Monkovic, I., Huang, S., and Balasubramanian, N., *Synth. Commun.* **25**, 2673 (1995).
16. Stingl, K., Kottenhahn, M., and Drauz, K., *Tetrahedron Asymmetry* **8**, 979 (1997).
17. Eichhorn, K., Roduit, J.-P., Shaw, N., Heinzmann, K., and Kiener, A., *Tetrahedron Asymmetry* **8**(15), 2533 (1997).
18. Fuchs, R., and Roduit, J.-P., U.S. Patent 5,886,181 (1996).
19. Kiener, A., Roduit, J.-P., Kohr, J., and Shaw, N., European Patent 0 686 698 (1995).
20. Kiener, A., Roduit, J.-P., and Heinzmann, K., WO Patent 96/35775 (1996).
21. Brieden, W., Roduit, J.-P., and Fuchs, R., U.S. Patent 6,111,106 (1999).
22. Watanabe, N., Sadao, A., and Kuranishi, H., U.S. Patent 5,922,873 (1998).
23. Murakami, H., Satoh, S., Tobiama, T., Sakai, K., and Nohira, H., U.S. Patent 5,792,869 (1995).
24. Rosen, K., Pye, P. J., Volante, R. P., and Reider, P. J., U.S. Patent 5,977,364 (1999).
25. Kuwano, R., and Ito, Y., *J. Org. Chem.* **64**, 1232 (1999).
26. Rosen, K., Weissman, S. A., Sager, J., Reamer, R. A., Askin, D., Volante, R. P., and Reider, P. J., *Tetrahedron Lett.* **36**, 6419 (1995).
27. Rosen, K., Pye, P. J., Volante, R. P., DiMichele, L. M., and Reider, P. J., *Tetrahedron Lett.* **39**, 6823 (1998).
28. Aebischer, B., Fray, P., Haerter, H. P., Herrling, P. L., Mueller, W., Olverman, H. J., and Watkins, J. C., *Helv. Chim. Acta* **72**, 1043 (1989).
29. Shiraiwa, T., Shinjo, K., and Korokawa, H., *Bull. Chem. Soc. Jpn.* **64**, 3251 (1991).
30. Mager, H. I. X., and Berends, W., *Recl. J. R. Neth. Chem. Soc.* **78**, 109 (1959).
31. Felder, E., Maffei, S., Pietra, S., and Pitrè, D., *Chimia* **13**, 263 (1959).
32. Felder, E., Maffei, S., Pietra, S., and Pitrè, D., *Helv. Chim. Acta* **43**, 888 (1960).
33. Melloni, P., Torre, A. D., Munari, S. D., Meroni, M., and Tonani, R., *Gazz. Chim. Ital.* **115**, 159 (1985).
34. Sahu, D. P., *Indian J. Chem. Sect. B* **37**, 1149 (1998).
35. Landau, R. N., Singh, U., Gortsema, F., Sun, Y., Gomolka, S. C., Lam, T., Futran, M., and Blackmond, D. G., *J. Catal.* **175**, 201 (1995).
36. Bigge, C. F., Hays, S. J., Novak, P. M., Drummond, J. T., Johnson, G., and Bobovski, T. P., *Tetrahedron Lett.* **30**, 5193 (1989).
37. Hu, L.-Y., Ryder, T. R., Nikam, S. S., Millerman, E., Szoke, B. G., and Rafferty, M. F., *Bioorg. Med. Chem. Lett.* **9**, 1121 (1999).
38. Hegedus, L., Hada, V., Tungler, A., Mathé, T., and Szepesy, L., *Appl. Catal.* **201**, 107 (2000).
39. Hada, V., Tungler, A., and Szepesy, L., *Appl. Catal.* **210**, 165 (2001).