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Enantiomers of (2*R**,3*R**)-1-methyl-5-oxo-2-phenyltetrahydro-1*H*-pyrrolidine-3-carboxylic acid as novel chiral resolving agents

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Abstract—A series of (2*R**,3*R**)-1-methyl-5-oxo-2-aryltetrahydro-1*H*-pyrrolidine-3-carboxylic acids were prepared and their structures were proven with X-ray crystallography. Racemic acid **5** has been resolved into enantiomers (2*S*,3*S*)-**5** and (2*R*,3*R*)-**5** by the formation of diastereomeric salts with brucine **9** and strychnidine **10**, respectively. The ability of these enantiomers to serve as chiral discriminating agents was demonstrated by the chromatographic separation of diastereomeric amides and esters. Also, some preliminary results on the enantioselective reduction of prochiral imines with sodium borohydride modified by (2*R*,3*R*)-**5** were collected.

1. Introduction

Many important low weight natural products, as well as enzymes, antibodies, and complex metabolic intermediates contain the carboxylate group whose anionic properties account for their specific biochemical profile.[1] On the other hand, chiral carboxylic acids of natural or synthetic origin are valuable tools for many optical activation methods.[2] In the field of asymmetric synthesis, several milestone methodologies have been developed on the basis of simple chiral adjuvants like tartaric or malic acids; for example, the Yamamoto asymmetric Diels–Alder reaction,[3] the Sharpless asymmetric epoxidation,[4] dihydroxylation[5] or oxyamination,[6] or Charette's asymmetric cyclopropanation.[7] Furthermore, modern supramolecular chemistry often investigates the host–guest interactions involving receptors with chiral acids incorporated in their structures.[8–10] This research was greatly influenced by the application of acids and their derivatives as chiral ligands or chiral discriminating agents. The TADDOLs developed by Seebach[11] are an excellent example of molecules whose structure can be fine-tuned to develop ligands of required properties (TADDOLates, see Roesky[12]). Simple and inexpensive carboxylic acids are also widely employed as chiral building blocks.[13,14] Among them, tartaric and malic acids are the leading commercial sources of chirality with (+)-(2*R*,3*R*)-tartaric acid (natural) being one of the most inexpensive enantiomerically pure compounds.[15] Despite a great amount of development of new procedures in the field of asymmetric synthesis, enantiomer separation by resolution[16] still remains a basic method in industry.[2,17] Again, the availability and price of chiral inductors are of considerable importance. However, many known chiral carboxylic acids are not fully satisfactory with regards to the solubility profile, susceptibility to racemization or other side reactions and low yield of the formation of their derivatives. Therefore, the search for optical activation promoters is still in demand. Herein, we report the synthesis and utility of both enantiomers of (2*R**,3*R**)-1-methyl-5-oxo-2-phenyltetrahydro-1*H*-pyrrolidine-3-carboxylic acid.

2. Results and discussion

Interactions between chiral molecules and the ability of a given substance to be a good resolving or solvating agent still need a precise theoretical description. However, simple models such as 'three-point interaction' model, first proposed by Pirkle,[18] can correctly account for many chiral recognition phenomena.[19,20] The molecule of

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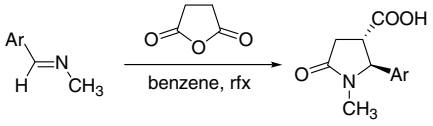
(2*R**,3*R**)-1-methyl-5-oxo-2-phenyltetrahydro-1*H*-pyrrolidine-3-carbox- ylic acid **5**, having an acidic site together with an aromatic ring and a hydrogen bond acceptor, appeared to be a good candidate for chiral discrimination processes. Also, a configurational stability of this compound might be expected due to the *trans* arrangement of the substituents. The racemic acid can be prepared according to the Castagnoli method[21] or following a more efficient microwave-assisted preparation.[22] In the original procedure,[21] the chemical yield was 82%, but it corresponded to the mixture of diastereomers from which (2*R**,3*R**)-isomer could be separated by repeated crystallizations in a yield not exceeding 32%. We found that when the reaction was terminated after 28 h, acid **5** could be separated as the sole product in 43% yield[23] (Scheme 1).



1 Ar= phenyl
2 Ar= 2-chlorophenyl
3 Ar= 4-methoxyphenyl
4 Ar= 3,4-methylenedioxyphenyl

5 Ar= phenyl 43%
6 Ar= 2-chlorophenyl 45%
7 Ar= 4-methoxyphenyl 61%
8 Ar= 3,4-methylenedioxyphenyl 65%

Scheme 1.

Attempts to use toluene instead of benzene increased the yield to 65%; however a slight but persistent contamination with the (2*R**,3*S**)-diastereomer[21] could be detected by ^{1}H NMR. The crystallographic properties of acid **5** have already been studied in our laboratory.[23] A similar procedure for the reaction with succinic anhydride could be applied for other *N*-[(*E*)-(aryl)-methylene]methanamines derived from the corresponding aromatic aldehydes and methylamine.

As a result, some additional analogues **6**–**8** of acid (2*R**,3*R**)-**5** were prepared (Scheme 1). The yields ranged from 43% to 65%. In several cases, we were able to obtain crystals suitable for X-ray analysis that served for the final proof for their structures (Figs. 1–3).

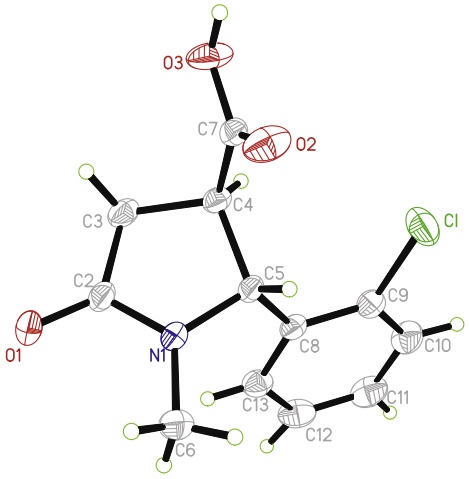


Figure 1. ORTEP diagram of racemic acid **6**.

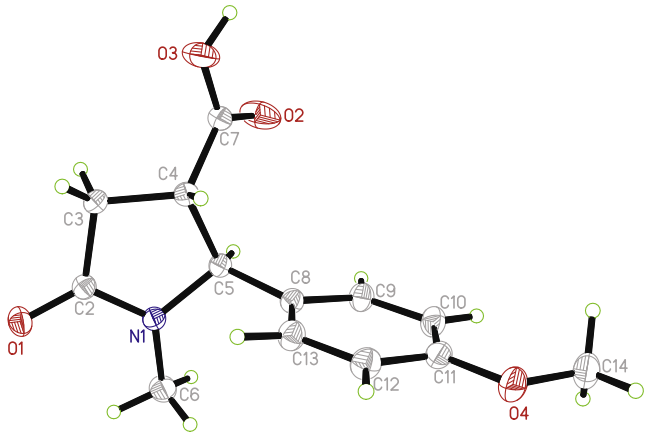


Figure 2. ORTEP diagram of racemic acid **7**.

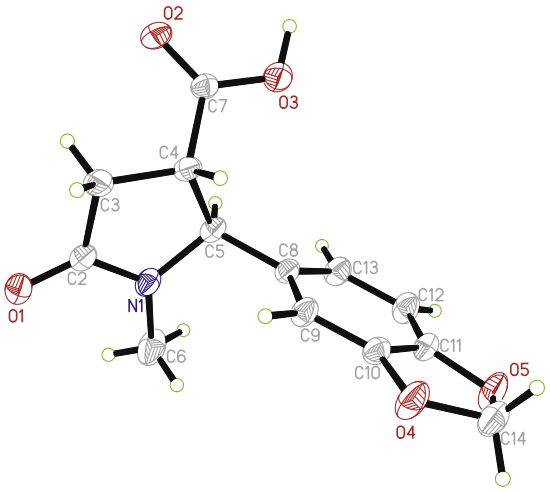
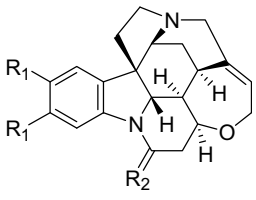


Figure 3. ORTEP diagram of racemic acid **8**.

The racemic acid (2*R**,3*R**)-**5** was subjected to the optical resolution method by the treatment with an equimolar amount of brucine **9** (Fig. 4) in 1-propanol. As a result, crystals of the salt of brucine and (2*S*,3*S*)-**5** acid deposited preferentially. The salt was recrystallized twice from the same solvent to afford an enantiomerically pure material from which compound (2*S*,3*S*)-**5** was finally obtained in 23% yield (based on the racemic acid **5**). The single crystal X-ray crystallography determined the absolute configuration of this compound (Fig. 5).



9 R_1= OCH_3, R_2= O
10 R_1= H, R_2= H_2

Figure 4. Structural diagrams of brucine **9** and strychnidine **10**.

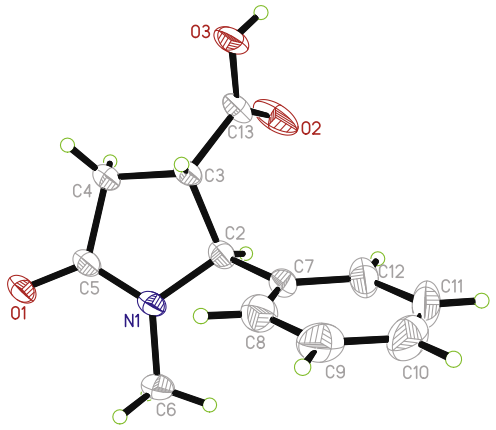


Figure 5. ORTEP diagram of acid (2*S*,3*S*)-**5**.

Interestingly, when racemic acid **5** was subjected to an analogous resolution procedure but using strychnidine **10**[24] instead of brucine **9** (Fig. 4) as a chiral base, the salt that crystallized out of the solution contained (2*R*,3*R*)-**5** as an acidic component. Again, a simple acid–base manipulation allowed us to isolate pure (2*R*,3*R*)-**5** in the crystalline form and in 28% yield [from (±)-**5**].[23] The yield of (2*R*,3*R*)-**5** was even higher (41%) when the mother liquor after the brucine-mediated resolution was worked up and was subjected to salt formation with strychnidine.

Such an unexpected behaviour of the resolving agents having a similar chirality sense was already observed by other investigators. In the mid-1980s, Walkinshaw and Gould[25] reported that the structures of the molecular complexes of brucine *N*-benzoyl-L-alaninate and strychnine (from which strychnidine **10** can be obtained by reduction) *N*-benzoyl-D-alaninate differ considerably in their spatial arrangement. Both the methoxy groups in the salt of brucine **9** caused the formation of cavities related by mirror symmetry to those present in the crystal of the strychnine salt.[25,26] Considering the fact that the crystal structure of some strychnidine **10** salts shows a similar self-assembly to strychnine molecular complexes,[27] the above observed behaviour of (2*R**,3*R**)-**5** with bases **9** and **10** seems to be better understood.

With both pure enantiomers of acid **5** in hands, we started the investigation of their possible use as chiral resolving agents. At first, the simple reaction of (2*S*,3*S*)-**5** with racemic α-phenylethylamine was chosen. Since we were not successful in the resolution based on solubility differences between the corresponding salts, we decided to make the covalently bound diastereomers. Thus, an equimolar mixture of (2*S*,3*S*)-**5** and *rac*-α-phenylethylamine was subjected to a BOP mediated coupling[28] in THF at 5 °C. The reaction was terminated when the entire amine component was consumed (12 h). The resulting mixture of diastereomeric amides proved to be easily separated using a column chromatography on silica-gel to afford pure components **11** and **12** in 39% and 42% yields, respectively (Scheme 2). The stereochemistry of both compounds was established by spectroscopic methods and the X-ray crystallography for compound **11** (Fig. 6).

To extend the utility of the novel chiral discriminating agent to other classes of compounds, we chose *rac*-benzoin as an example of a chiral alcohol. Since the coupling reaction between benzoin and (2*S*,3*S*)-**5** under the same conditions as in the case of α-phenylethylamine proceeded with a very low yield along with the formation of several by-products, we started the optimization procedure. The use of *N*,*N*-dicyclohexylocarbodiimide (DCC) in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) proved to be the best synthetic choice and both esters **13** and **14** were formed without extensive decomposition (Scheme 3).

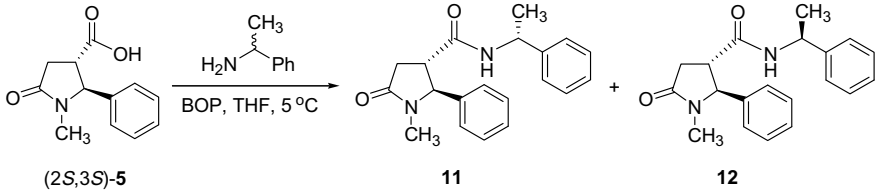
Compounds **13** and **14** were then separated using column chromatography in 39% and 37% yields, respectively. Mild ammonolysis of the esters afforded both enantiomers of benzoin that were >95% ee.

Another racemic alcohol was also successfully resolved via the formation of diastereomeric esters with (2*S*,3*S*)-**5**. Thus, *rac*-**15**[29] was reacted with (2*S*,3*S*)-**5** in the presence of DCC to afford a mixture of esters **16** and **17** (Scheme 4). Both compounds were separated by column chromatography giving pure components, which, after mild, base-catalysed hydrolysis, gave enantiomers (*S*)-(−)-**15** and (*R*)-(+)-**15** in enantiomerically pure forms with the yields of 33% and 38%, respectively.

Additionally, enantiomer (*R*)-(+)-**15** could also be obtained in the form of a monocrystal that allowed us to assign the absolute configuration by means of the X-ray study (Fig. 7).

It should also be noted here that acid (2*S*,3*S*)-**5** can be recovered after the above resolution process without any loss of its enantiomeric purity.

Chiral carboxylic acids also appear to be useful in some enantioselective reactions. In 1979, Iwakuma reported the use of sodium (*S*)-prolinate-borane complex, prepared from sodium borohydride and L-proline, to the asymmetric reduction of prochiral ketones to optically active alcohols[30]



(2*S*,3*S*)-**5** **11** **12**

Scheme 2.

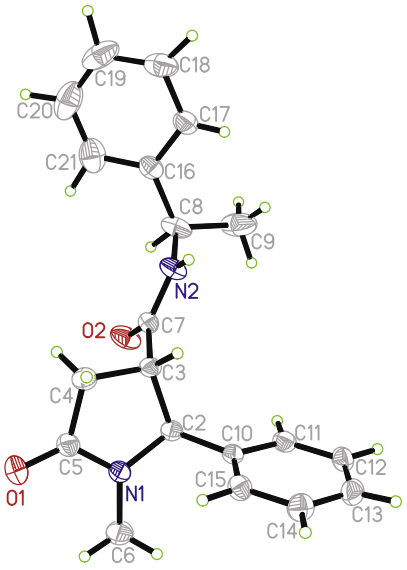


Figure 6. ORTEP diagram of amide **11**.

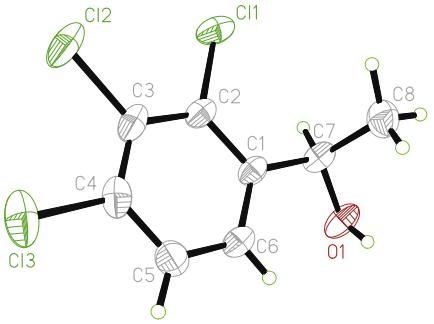
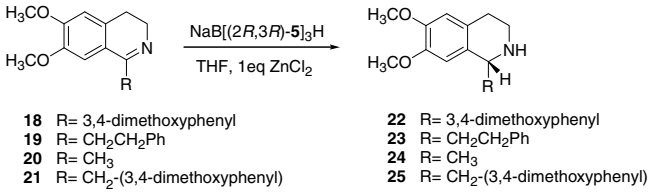


Figure 7. ORTEP diagram of alcohol (*R*)-(+)-**15**.



18 R= 3,4-dimethoxyphenyl
19 R= CH_2CH_2Ph
20 R= CH_3
21 R= CH_2-(3,4-dimethoxyphenyl)

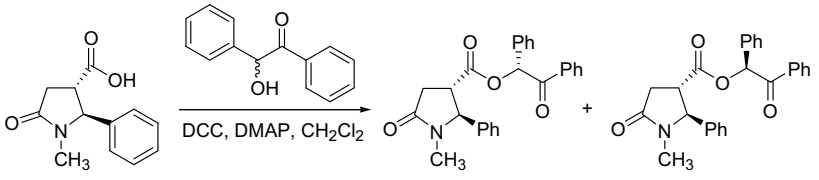
22 R= 3,4-dimethoxyphenyl
23 R= CH_2CH_2Ph
24 R= CH_3
25 R= CH_2-(3,4-dimethoxyphenyl)

Scheme 5.

and also of cyclic imines to chiral non-racemic secondary amines.[31] The same idea was later explored by Hajipour and Hantehzadeh[32] who applied sodium borohydride modified with *N*,*N*-phthaloyl-amino acids to the enantioselective addition to the imine double bond. On the basis of the above literature examples, we decided to prepare an analogous tri-acyloxyborohydride by the reaction of $NaBH_4$ with 3 equiv of acid (2*R*,3*R*)-**5**. The reaction of this reducing agent with imines **18**–**21** proceeded with good chemical yield but with rather low enantioselectivity (<10% ee). However, when 1 equiv of $ZnCl_2$ was introduced to the reaction mixture,[32] the enantiomeric output of this reaction was slightly improved apparently due to the complexation of the imine molecule with the reducing agent[32] (Scheme 5, Table 1).

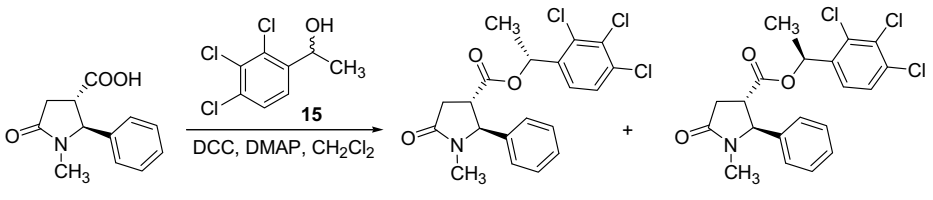
3. Conclusions

In conclusion, we have prepared a series of (2*R**,3*R**)-1-methyl-5-oxo-2-aryltetrahydro-1*H*-pyrrolidine-3-carboxylic acids and proved their structures by structural analysis. The racemic acid **5** has been resolved into enantiomers (2*S*,3*S*)-**5** and (2*R*,3*R*)-**5** by the formation of their salts with brucine **9** and strychnidine **10**, respectively. The ability of chiral discrimination was demonstrated for both enantiomers by the separation of diastereomeric amides and esters. Also, some preliminary results were collected on the enantioselective reduction of prochiral imines with sodium borohydride modified by (2*R*,3*R*)-**5**.



(2*S*,3*S*)-**5** **13** **14**

Scheme 3.



(2*S*,3*S*)-**5** **16** **17**

Scheme 4.

Table 1. Reductions of imines **18**–**21** with modified borohydride

Entry	Imine	Amine	Yield (%)	Enantiomeric excess (%)	Configuration
1	**18**	**22**	86.2	11.9	(*R*)
2	**19**	**23**	85.2	4.1	(*R*)
3	**20**	**24**	78.9	5.0	(*R*)
4	**21**	**25**	90.3	21.5	(*R*)

4. Experimental

The NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 500 MHz (or 200 MHz) for ^{1}H NMR and at 125 MHz (or 50 MHz) for ^{13}C NMR. The spectra were measured in $CDCl_3$, DMSO-d_6, pyridine-d_5 and are given as δ values (in ppm) relative to TMS. Mass spectra were collected on Quatro LC Micromass and LCT Micromass TOF HiRes apparatus. Optical rotation was measured on a Perkin–Elmer 247 MC polarimeter. TLC analyses were performed on silica gel plates (Merck Kiesegel GF_{254}) and visualized using UV light or iodine vapour. Column chromatography was carried out at an atmospheric pressure using Silica Gel 60 (230–400 mesh, Merck) using mixtures of chloroform/methanol or cyclohexane/ethyl acetate as eluents. HPLC analyses were performed on a Knauer (model 64) apparatus with Eurochrom 2000 software using 4 mm × 250 mm silica (5 μm) column. Chiral HPLC analyses were done using a ChiraSep® (DNBPG) column from Merck with hexane/2-propanol 95:5 (v/v) or ChiraDex® column (Merck) with methanol/water 4:1 (v/v) as eluent. For better separation, the columns were cooled to 10 °C. Melting points were determined on a Boetius hot-plate microscope and are uncorrected. All solvents used in the reactions were anhydrous. Most of the single crystal X-ray measurements were done on a KUMA KM4 CCD κ-axis diffractometer with point scintillation counter using Mo Kα radiation but data for (2*S*,3*S*)-**5** were collected using Cu Kα radiation on the Oxford Diffraction Xcalibur κ-axis diffractometer with the Ruby ccd detector. The use of copper radiation together with collecting data for Friedel pairs for all reflections enabled to determine the absolute structure for the latter. After initial corrections and data reduction, intensities of reflections were used to solve and consecutively refine structures using SHELXS 97[33] and SHELXL 97[34] programs.

4.1. General procedure for the preparation of racemic acids 5–8

A solution of 10.0 g (0.1 mmol) of succinic anhydride and 0.1 mol of the appropriate *N*-arylmethylenemethanamine was refluxed in 250 mL of benzene under argon for 28 h. The reaction mixture was then cooled and extracted with sat. $KHCO_3$ solution (4 × 50 mL). The combined aqueous phase was washed with benzene (2 × 40 mL) and acidified carefully with *o*-phosphoric acid to approx. pH 2. The crude product was deposited in the form of crystals or solidifying oil upon 12 h storage in the refrigerator at 5 °C. The collected solid material was recrystallized from water (twice) or dried and recrystallized from organic solvent.

4.1.1. (2*R,3*R**)-1-Methyl-5-oxo-2-phenyltetrahydro-1*H*-pyrrolidine-3-carboxylic acid 5.** Starting from *N*-[(1*E*)-phenylmethylene]methanamine **1**,[35] acid (2*R**,3*R**)-**5** was obtained in 43% yield after recrystallization from boiling water (2×). White solid. Mp: 127–128 °C. Spectral data were in agreement with the literature values.[21]

The detailed structural parameters have been deposited with the Cambridge Crystallographic Data Centre under the number CCDC 197134.

4.1.2. (2*R,3*R**)-2-(2-Chlorophenyl)-1-methyl-5-oxotetrahydro-1*H*-pyrrolidine-3-carboxylic acid 6.** Starting from *N*-[(1*E*)-(2-chlorophenyl)methylene]methanamine **2**,[36] acid (2*R**,3*R**)-**6** was obtained in 45% yield after recrystallization from acetone (2×). White solid. Mp: 175–178 °C. ^{1}H NMR (200 MHz, DMSO-d_6) $\delta = 7.19$–7.55 (m, 4H, H_{arom}), 5.17 (d, 1H, H-2, $J = 4.0$ Hz), 4.80 (br s, COOH), 2.93–3.03 (m, 1H, H-3), 2.51 (s, 3H, NCH_3), 2.44–2.46 and 2.67–2.80 (two m, 2H, H-4); ^{13}C NMR (50 MHz, DMSO-d_6) $\delta = 173.9$, 172.3, 136.5, 132.2, 130.0, 129.6, 127.8, 62.7, 43.8, 32.9, 27.7; ESI MS (positive) *m*/*z*: 254.0 $[M+H]^+$, 276.0 $[M+Na]^+$, 529.1 $[2M+Na]^+$; ESI MS (negative) *m*/*z*: 252.0 $[M-H]^-$, 505.1 $[2M-H]^-$; HR MS: calcd for $C_{12}H_{12}NO_3Cl$ 253.6816, found 253.6818.

The detailed structural parameters have been deposited with the Cambridge Crystallographic Data Centre under the number CCDC 660967.

4.1.3. (2*R,3*R**)-2-(4-Methoxyphenyl)-1-methyl-5-oxotetrahydro-1*H*-pyrrolidine-3-carboxylic acid 7.** Starting from *N*-[(1*E*)-(4-methoxyphenyl)methylene]methanamine **3**,[35] acid (2*R**,3*R**)-**7** was obtained in 61% yield after recrystallization from acetone (2×). White solid. Mp: 186–189 °C. ^{1}H NMR (200 MHz, pyridine-d_5) $\delta = 7.33$ (d, 2H, $J = 8.8$ Hz, H_{arom}), 7.23 (br s, 1H, COOH), 7.02 (d, 2H, $J = 8.8$ Hz, H_{arom}), 5.03 (d, 1H, $J = 5.6$ Hz, H-2), 3.72 (s, 3H, OCH_3), 3.30–3.41 (m, 1H, H-3), 3.09–3.14 (m, 2H, H-4), 2.70 (s, 3H, NCH_3); ^{13}C NMR (50 MHz, pyridine-d_5) $\delta = 175.4$, 173.1, 160.0, 132.8, 128.6, 114.8, 66.5, 55.3, 47.2, 34.4, 28.1; ESI MS (positive) *m*/*z*: 250.1 $[M+H]^+$, 272.1 $[M+Na]^+$, 521.2 $[2M+Na]^+$; ESI MS (negative) *m*/*z*: 248.1 $[M-H]^-$, 497.2 $[2M-H]^-$; HR MS: calcd for $C_{13}H_{15}NO_4$ 249.2625, found 249.2630.

The detailed structural parameters have been deposited with the Cambridge Crystallographic Data Centre under the number CCDC 660968.

4.1.4. (2*R,3*R**)-2-(1,3-Benzodioxol-5-yl)-1-methyl-5-oxotetrahydro-1*H*-pyrrolidine-3-carboxylic acid 8.** Starting from *N*-[(1*E*)-1,3-benzodioxol-5-ylmethylene]methanamine

4,[37] acid (2*R**,3*R**)-**8** was obtained in 65% yield after recrystallization from 1-propanol (2×). White solid. Mp: 216–220 °C. ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 12.70$ (br s, 1H, COOH), 6.86–6.93 and 6.75–6.80 (2× m, 3H, H_{arom}), 6.03 (s, 2H, OCH_2O), 4.62 (d, 1H, $J = 6.0$ Hz, H-2), 2.94–3.06 (m, 1H, H-3), 2.48–2.79 (m, 2H, H-4), 2.47 (s, 3H, NCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 173.7$, 171.8, 147.8, 147.0, 133.8, 120.7, 108.2, 106.8, 101.1, 65.4, 45.1, 33.1, 27.4; ESI MS (positive) *m*/*z*: 264.1 $[M+H]^+$, 286.0 $[M+Na]^+$; ESI MS (negative) *m*/*z*: 262.1 $[M-H]^-$, 525.1 $[2M-H]^-$; HR MS: calcd for $C_{13}H_{13}NO_5$ 263.2460, found 263.2461.

The detailed structural parameters have been deposited with the Cambridge Crystallographic Data Centre under the number CCDC 660970.

4.2. Resolution of racemic acid 5

A hot solution of 7 g (31 mmol) of (2*R**,3*R**)-**5** in 5 mL of 1-propanol was combined carefully with a hot solution of brucine **9** or strychnidine **10** (31 mmol) in 8 mL of 1-propanol and the resulted mixture was boiled for 5 min and left for slow crystallization during 24 h. The deposited crystals were then filtered off, washed with cold 1-propanol and recrystallized from boiling 1-propanol until a constant melting point and the specific rotation values were reached.

Data for the salt of (2*S*,3*S*)-**5** with brucine **9**: Yield 27%; mp 219–221 °C; $[\alpha]_D^{22} = +21.1$ (*c* 1.8, $CHCl_3$).

Data for the salt of (2*R*,3*R*)-**5** with strychnidine **10**: Yield 31%; mp 115–118 °C; $[\alpha]_D^{22} = -55.8$ (*c* 1.8, $CHCl_3$).

The salt (10 mmol) was then introduced gradually to the stirred two-phase mixture of 60 mL of methylene chloride and 60 mL of 20% $NaOH_{aq}$. The aqueous layer was then extracted with CH_2Cl_2 (4 × 25 mL) and carefully acidified to pH 1–2 with 10% HCl_{aq} at the temperature not exceeding 15 °C. After extraction with CH_2Cl_2 (5 × 20 mL), washing the combined extract with brine (3 × 25 mL), drying and evaporating, the enantiomeric form of acid **5** was obtained. Subsequent crystallization from 1-propanol afforded a pure product.

4.2.1. (2*S*,3*S*)-1-Methyl-5-oxo-2-phenyltetrahydro-1*H*-pyrrolidine-3-carboxylic acid (+)-5. Yield (23%) from the racemate; mp 150–152 °C; $[\alpha]_D^{22} = +112.0$ (*c* 0.9, $CHCl_3$). The enantiomeric purity of **5** (>98% ee) was established on the basis of HPLC analysis on chiral stationary phase (DNBPG column) after derivatization with an ether solution of diazomethane.

The crystal structure of (2*S*,3*S*)-**5** is both chiral and polar. The main structural motifs of it are parallel polar hydrogen bonded chains of molecules passing in the *b*-direction. The molecules are bonded via O–H···O hydrogen bonds between carboxyl O–H group and carbonyl oxygen that distinguishes structure of this enantiomerically pure acid from the remaining racemates, where centrosymmetric hydrogen bonded dimers were observed. The 0.0(3) value of the Flack[38] parameter confirms the correctness of the absolute structure and hence the absolute configuration of the molecule.

The detailed structural parameters have been deposited with the Cambridge Crystallographic Data Centre under the number CCDC 660971.

4.2.2. (2*R*,3*R*)-1-Methyl-5-oxo-2-phenyltetrahydro-1*H*-pyrrolidine-3-carboxylic acid (−)-5. Yield (28%) from the racemate; mp 149–151 °C; $[\alpha]_D^{22} = -106$ (*c* 1.0, $CHCl_3$), >93% ee upon comparison of the specific rotation value for its enantiomer.

4.3. Reaction of (2*S*,3*S*)-5 with racemic α-phenylethylamine

A mixture of 810 mg (3.7 mmol) of (2*S*,3*S*)-**5**, α-phenylethylamine (0.48 mL, 3.7 mmol) and BOP (Castro's reagent[28]; 1.8 g, 4 mmol) in 15 mL of dry THF was stirred under an argon atmosphere at 5 °C. To this mixture, triethylamine (0.8 g, 7.3 mmol) was added drop wise with vigorous stirring. The stirring was continued for 12 h and the solvent was then evaporated under reduced pressure. The residue was quenched with CH_2Cl_2 (30 mL) and the organic phase was washed with brine (4 × 30 mL). After drying over anhydrous Na_2SO_4, the solvent was evaporated and the residue was subjected to column chromatography using $CHCl_3/CH_3OH$ (98:2, v/v) as eluent to afford two diastereomeric amides **11** and **12**.

4.3.1. (2*S*,3*S*)-1-Methyl-5-oxo-2-phenyl-*N*-[(1*R*)-1-phenylethyl]tetrahydro-1*H*-pyrrolidine-3-carboxoamide 11. Yield of 465 mg (39%). Colourless crystals. Mp 148–149 °C; $[\alpha]_D^{22} = +71.7$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 7.42$–7.45 (m, 2H, H_{arom}), 7.36–7.40 (m, 1H, H_{arom}), 7.29–7.32 (m, 2H, H_{arom}), 7.23–7.25 (m, 3H, H_{arom}), 7.19–7.21 (m, 2H, H_{arom}), 5.49 (d, 1H, $J = 8.0$ Hz, NH), 5.10 (m, 1H, $J = 7.0$ Hz, PhC*H*(CH_3)N), 4.66 (d, 1H, $J = 9.5$ Hz, H-2), 2.85–2.90 and 2.71–2.76 (2× m, 2H, H-4), 2.65–2.68 (m, 1H, H-3), 2.64 (s, 3H, NCH_3), 1.41 (d, 3H, $J = 6.5$ Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 173.5$, 169.8, 142.4, 139.5, 129.3, 128.8, 128.8, 127.6, 126.9, 126.1, 67.5, 49.2, 49.0, 34.2, 28.4, 21.6; ESI MS (positive) *m*/*z*: 345.1 $[M+Na]^+$, 667.3 $[2M+Na]^+$; HR MS: calcd for $C_{20}H_{22}N_2O_2$ 322.4009, found 322.4012.

The detailed structural parameters have been deposited with the Cambridge Crystallographic Data Centre under the number CCDC 660969.

4.3.2. (2*S*,3*S*)-1-Methyl-5-oxo-2-phenyl-*N*-[(1*S*)-1-phenylethyl]tetrahydro-1*H*-pyrrolidine-3-carboxoamide 12. Yield of 501 mg (42%). Colourless crystals. Mp 200–202 °C; $[\alpha]_D^{22} = -10.3$ (*c* 1.0, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 7.26$–7.35 and 7.05–7.17 (2× m, 10H, H_{arom}), 5.82 (br s, 1H, NH), 5.11 (m, 1H, PhC*H*(CH_3)N), 4.53 (d, 1H, $J = 7.5$ Hz, H-2), 2.85–2.94 and 2.62–2.70 (2× m, 2H, H-4), 2.74–2.79 (m, 1H, H-3), 2.57 (s, 3H, NCH_3), 1.41 (d, 3H, $J = 6.5$ Hz, CH_3,); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 173.6$, 170.0, 142.8, 139.3, 129.2, 128.7, 128.6, 127.4, 126.8, 126.1, 67.6, 49.0, 34.3, 28.3, 21.5; ESI MS (positive) *m*/*z*: 345.1 $[M+Na]^+$, 667.3 $[2M+Na]^+$; HR MS: calcd for $C_{20}H_{22}N_2O_2$ 322.4009, found 322.4017.

4.4. Reaction of (2*S*,3*S*)-5 with racemic benzoin

(2*S*,3*S*)-1-Methyl-5-oxo-2-phenyltetrahydro-1*H*-pyrrolidine-3-carboxylic acid **5** (219 mg, 1 mmol), *rac*-benzoin (212 mg, 1 mmol) and DMAP (30.5 mg, 0.25 mmol) were dissolved in dry CH_2Cl_2 (10 mL) under argon and the mixture was stirred for 10 min. After cooling to 0 °C, DCC (309 mg, 1.5 mmol) was added and the reaction mixture was stirred for 12 h at room temperature. The DCU precipitate was filtered off and the solvent was evaporated under vacuum. The residue was taken up in CH_2Cl_2 and washed twice with 0.5 N HCl, then dried over $MgSO_4$. The solvent was evaporated and the residue was subjected to column chromatography using CH_2Cl_2/CH_3OH (99:1, v/v) as eluent to afford two diastereomeric esters **13** and **14**.

4.4.1. (1*R*)-2-Oxo-1,2-diphenyl-ethyl (2*S*,3*S*)-1-methyl-5-oxo-2-phenyltetrahydro-1*H*-pyrrolidine-3-carboxylate 13. Yield of 161 mg (39%). $[\alpha]_D^{22} = -34.2$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 7.90$ (m, 2H, H_{arom}), 7.51 (m, 1H, H_{arom}), 7.36 (m, 10H, H_{arom}), 7.23 (m, 2H, H_{arom}), 6.85 (s, 1H, PhCHC=O), 4.86 (d, 1H, $J = 6.0$ Hz, H-2), 3.21 (m, 1H, H-3), 2.96 (m, 2H, H-4), 2.68 (s, 3H, NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 193.0$, 172.7, 171.8, 139.2, 134.4, 133.7, 132.9, 129.6, 129.2, 129.1, 128.8, 128.7, 128.7, 128.5, 126.7, 78.4, 66.2, 46.1, 33.6, 28.3; ESI MS (positive) *m*/*z*: 436 $(M+Na)^+$, 849 $(2M+Na)^+$; HR MS: calcd for $C_{26}H_{23}NO_4$ 413.4651, found 413.4647.

4.4.2. (1*S*)-2-Oxo-1,2-diphenyl-ethyl (2*S*,3*S*)-1-methyl-5-oxo-2-phenyltetrahydro-1*H*-pyrrolidine-3-carboxylate 14. Yield of 153 mg (37%). $[\alpha]_D^{22} = +150.8$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 7.93$ (m, 2H, H_{arom}), 7.53 (m, 1H, H_{arom}), 7.38 (m, 12H, H_{arom}), 6.88 (s, 1H, PhCHC=O), 4.99 (d, 1H, $J = 5.0$ Hz, H-2), 3.21 (m, 1H, H-3), 2.87 and 2.86 (2× m, 2H, H-4), 2.71 (s, 3H, NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 193.5$, 173.1, 172.2, 139.8, 134.5, 133.9, 133.0, 129.7, 129.4, 129.3, 129.0, 128.9, 128.9, 128.7, 126.9, 78.6, 66.7, 45.7, 33.0, 28.6; ESI MS (positive) *m*/*z*: 436 $(M+Na)^+$, 849 $(2M+Na)^+$; HR MS: calcd for $C_{26}H_{23}NO_4$ 413.4651, found 413.4654.

4.5. Hydrolysis of esters 13 and 14

To a solution of 100 mg (0.24 mmol) of ester **13** or **14** in 10 mL of methanol, 0.25 mL of NH_{3aq} was added and the reaction mixture was stirred at room temperature until all substrates were consumed (TLC, approx. 1 h). After subsequent addition of 0.1 mL of glacial acetic acid, the solvent was evaporated and the residue was taken up into benzene (10 mL) and the organic layer was washed with brine (3 × 10 mL). After drying over anhydrous Na_2SO_4 and evaporation of the solvent, the residue was chromatographed on silica-gel (CH_2Cl_2) to afford optically active benzoin.

4.5.1. (*R*)-(−)-Benzoin. The title compound was obtained from ester **13** in 95% yield.

Mp 132–134 °C, $[\alpha]_D^{22} = -110.4$ (*c* 1.3, acetone); lit.[39]: mp 135–137 °C, $[\alpha]_D^{22} = -115$ (*c* 1.5, acetone).

4.5.2. (*S*)-(+)-Benzoin. The title compound was obtained from ester **14** in 91% yield.

Mp 133–134 °C, $[\alpha]_D^{22} = +109.2$ (*c* 1.3, acetone); lit.[39]: mp 135–137 °C, $[\alpha]_D^{22} = +115$ (*c* 1.5, acetone).

4.6. Reaction of (2*S*,3*S*)-5 with racemic 1-(2,3,4-trichlorophenyl)ethanol 15

A mixture of 243 mg (1.1 mmol) of acid (2*S*,3*S*)-**5** and 250 mg (1.1 mmol) of racemic 1-(2,3,4-trichlorophenyl)ethanol **15**[29] and 34 mg (0.28 mmol) of DMAP in 10 mL of dry CH_2Cl_2 was stirred under argon for 10 min at room temperature. After cooling to 0 °C, a sample of 343 mg (1.7 mmol) of DCC was introduced in one portion and the mixture was stirred at 0 °C for 2 h. The precipitate of DCU was then filtered off and the solution was washed twice with 1% HCl_{aq} and brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was subjected to column chromatography on silica-gel using cyclohexane/ethyl acetate (9:1, v/v) as eluent.

4.6.1. (1*R*)-1-(2,3,4-Trichlorophenyl)ethyl (2*S*,3*S*)-1-methyl-5-oxo-2-phenyltetrahydro-1*H*-pyrrolidine-3-carboxylate 16. A less polar diastereomer was isolated in 38% yield in the form of oil.

$[\alpha]_D^{22} = +36.7$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.33$–7.45 (m, 4H, H_{arom}), 7.13–7.27 (m, 2H, H_{arom}), 7.08 (d, 1H, $J = 8.3$ Hz, CHCCl), 6.19 (q, 1H, $J = 6.5$ Hz, PhCHC=O), 4.76 (d, 1H, $J = 6.0$ Hz, H-2), 3.13 (m, 1H, H-3), 2.80 (dd, 2H, $^1J = 14.0$ Hz, $^2J = 8.2$ Hz, H-4), 2.67 (s, 3H, NCH_3), 1.49 (d, 3H, J=6.5 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 175.2$, 171.2, 139.8, 139.3, 133.8, 132.3, 129.5, 128.9, 126.9, 126.9, 124.6, 70.7, 66.6, 46.4, 33.6, 25.1, 21.0; ESI MS (positive) *m*/*z*: 448 $(M+Na)^+$.

4.6.2. (1*S*)-1-(2,3,4-Trichlorophenyl)ethyl (2*S*,3*S*)-1-methyl-5-oxo-2-phenyltetrahydro-1*H*-pyrrolidine-3-carboxylate 17. A more polar diastereomer was isolated in 42% yield in the form of an amorphous solid. $[\alpha]_D^{22} = +49.5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.33$–7.46 (m, 3H, H_{arom}), 7.12–7.22 (m, 2H, H_{arom}), 7.31 (d_{AB}, 1H, $J =$ 8.4 Hz, C*H*CHCCl), 6.98 (d_{AB}, 1H, $J = 8.4$ Hz, CHCCl), 6.21 (q, 1H, $J = 6.4$ Hz, PhCHC=O), 4.68 (d, 1H, $J =$ 6.0 Hz, H-2), 3.12 (td, 1H, $^1J = 8.8$ Hz, $^2J = 6.0$ Hz, H-3), 2.85 (dd, 2H, $^1J = 8.8$ Hz, $^2J = 5.0$ Hz, H-4), 2.66 (s, 3H, NCH_3), 1.49 (d, 3H, $J = 6.4$ Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 172.7$, 171.5, 139.7, 139.1, 133.7, 132.1, 129.5, 129.0, 128.8, 126.9, 124.8, 70.8, 66.8, 46.6, 34.0, 28.5, 20.9; ESI MS (positive) *m*/*z*: 448 $(M+Na)^+$.

4.7. (1*R*)-1-(2,3,4-Trichlorophenyl)ethanol (*R*)-(+)-15

To a solution of 75 mg (0.176 mmol) of ester **16** in 10 mL of methanol, a solution of 20% KOH_{aq} (0.2 mL) was added and the mixture was stirred for 30 min at room temperature. The solvent was then evaporated and the mixture was quenched with 10 mL of CH_2Cl_2 and 10 mL of water. The organic layer was washed with water (2 × 2 mL), dried and evaporated to leave (*R*)-(+)-**15** as an amorphous solid

in 33% yield from *rac*-**15**. The detailed structural parameters have been deposited with the Cambridge Crystallographic Data Centre under the number CCDC 668012.

Mp 68–69 °C, $[\alpha]_D^{22} = +62.0$ (*c* 1.0, $CHCl_3$); The enantiomeric purity of **5** (>98% ee) was established on the basis of HPLC analysis on chiral stationary phase (ChiraDex column). ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.38$–7.51 (m, 2H, H_{arom}), 5.25 (q, 1H, $J = 6.4$ Hz), 2.07 (br s, 1H, OH), 1.46 (d, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 144.1$, 132.8, 131.8, 131.4, 128.8, 124.9, 67.6, 23.7; ESI MS (positive) *m*/*z*: 248 $(M+Na)^+$.

The combined aqueous phase was acidified to pH 2 with *o*-phosphoric acid and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine and evaporated after drying over anhydrous $MgSO_4$. The crystallization of the remaining solid from hot water afforded the recovered compound (2*S*,3*S*)-**5** (27 mg). Mp 151–152 °C; $[\alpha]_D^{22} = +112$ (*c* 0.9, $CHCl_3$).

(1*S*)-1-(2,3,4-Trichlorophenyl)ethanol (*S*)-(−)-**15** was obtained from ester **17**, according to the same procedure as described above. Yield (38%) from *rac*-**15**; Mp 68–69 °C, $[\alpha]_D^{22} = -60.4$ (*c* 1.0, $CHCl_3$). The spectral data were the same as for (*R*)-(+)-**15**.

4.8. Reduction of imines by sodium borohydride modified by (2*R*,3*R*)-5

The solution of the reducing agent was prepared by the addition of 100 mg (0.46 mmol) of acid (2*R*,3*R*)-**5** to the suspension of 58 mg (0.15 mmol) of sodium borohydride in 5 mL of dry THF under argon atmosphere. The reaction mixture was then stirred for 4 h at room temperature followed by the addition of 22 mg (0.16 mmol) of freshly fused $ZnCl_2$. After additional stirring for 1 h at room temperature, a sample of 0.4 mmol of imine **18**,[40] **19**,[41] **20**[42] or **21**[43] in 2 mL of dry THF was added via a syringe in one portion and the mixture was stirred overnight and finally refluxed for 1 h. After cooling to the ambient temperature, 1 mL of 30% $NaOH_{aq}$ was added and the mixture was evaporated to dryness. Methylene chloride (5 mL) was added to the residue together with 5 mL of water. The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated and the residue was chromatographed on silica-gel to afford the appropriate amine.

4.8.1. (1*R*)-1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 22. Yield of 113.4 mg (86.2%); oil; $[\alpha]_D^{22} = +4.4$ (*c* 1.0, $CHCl_3$), 11.9% ee; lit.[44]: $[\alpha]_D^{18} = -37.0$ (*c* 0.26, $CHCl_3$).

Spectral data were in agreement with the literature values.[44] The TLC properties were the same as for the authentic sample of this compound.

4.8.2. (1*R*)-6,7-Dimethoxy-1-(2-phenylethyl)-1,2,3,4-tetrahydroisoquinoline 23. Yield of 99.9 mg (85.2%); oil; $[\alpha]_D^{22} = +1.0$ (*c* 1.0, CH_3OH), 4.1% ee; lit.[45]: $[\alpha]_D^{25} = -24.5$ (*c* 0.77, CH_3OH).

Spectral data were in agreement with the literature values.[45] The TLC properties were the same as for the authentic sample of this compound.

4.8.3. (1*R*)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline 24. Yield of 89.3 mg (78.9%); oil; $[\alpha]_D^{22} = +3.0$ (*c* 1.1, $CHCl_3$), 5.0% ee; lit.[32]: $[\alpha]_D^{25} = -59.5$ (*c* 1.0, $CHCl_3$).

Spectral data were in agreement with the literature values.[32] The TLC properties were the same as for the authentic sample of this compound.

4.8.4. (1*R*)-1-(3,4-Dimetoxybenzyl)-6,7-dimetoxy-1,2,3,4-tetrahydroisoquinoline 25. Yield 136.3 mg (90.3%); oil; $[\alpha]_D^{22} = +6.2$ (*c* 1.0, $CHCl_3$), 21.5% ee; lit.[46]: $[\alpha]_D^{25} = -28.8$ (*c* 1.1, $CHCl_3$).

Spectral data were in agreement with the literature values.[46] The TLC properties were the same as for authentic sample of this compound.

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