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Chiral solvating properties of (*S*)-1-benzyl-6-methylpiperazine-2,5-dione

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Abstract—In $CDCl_3$ solution, enantiopure (*S*)-1-benzyl-6-methylpiperazine-2,5-dione (*S*)-**1a** formed diastereomeric C=*O*···*H*–N hydrogen-bonded associates with racemic (*RS*,*Z*)-1-benzyl-3-[(dimethylamino)methylidene]piperazine-2,5-diones **2a** and **2b**, (*RS*)-*tert*-butyl pyroglutamate (*RS*)-**2c** and (*RS*)-*N*-benzoylalanine methyl ester (*RS*)-**2d**. This resulted in splitting (doubling) of the characteristic signals in the ^{1}H NMR and ^{13}C spectra of racemic compounds **2a**–**d** in the presence of 1 equiv of (*S*)-**1a**. The formation of hydrogen-bonded dimers in $CDCl_3$ solution was studied by ^{1}H NMR, ^{13}C NMR and 2D NMR and confirmed by the intermolecular NOE observed between the hydrogen-bonded amide protons from each of the monomeric units, (*S*)-**1a** and **2a**–**c**. On the other hand, a slightly different binding mode was proposed for association of (*S*)-**1a** with alaninamide (*RS*)-**2d**. Enantiomer compositions of known (weighed) mixtures of both enantiomers of *tert*-butyl pyroglutamate **2c** were re-determined by ^{1}H NMR in the presence of (*S*)-**1a** in $CDCl_3$. The experimental values were in good agreement with the theoretical values, thus indicating the potential applicability of (*S*)-**1a** and related diketopiperazines as chiral solvating agents in NMR spectroscopy.

1. Introduction

Over the years, numerous methods for the determination of the enantiomeric purity of chiral compounds have been developed. Among them, NMR spectroscopy represents one of the most common ways for the determination of the ee and absolute configuration, using either a chiral derivatization and/or a chiral solvation strategy. Various fluorinated α-hydroxymethylidenecamphor-based lanthanide shift reagents are nowadays commonly used reagents for the determination of ee and absolute configuration.[1–3] In addition to lanthanide shift reagents, chiral solvation agents (CSA) that are not covalently attached to the enantiomers, for example, carboxylic acids,[4] 1,1′-(anthracene-9,10-diyl)bis(2,2,2-trifluoro-ethanol),[5] cyclodextrins,[6] crown ethers,[7] calixarenes,[8] binaphthyls,[9] α-amino acid derivatives[10] and porphyrins,[11] have also been successfully employed for the determination of enantiomeric purity and absolute configuration.

Binding of amino acids via C=*O*···*H*–N hydrogen bonds is one of the most important features in the secondary structure of peptides and proteins.[12] Diketopiperazines (piperazine-2,5-diones) are an important and useful class of heterocyclic compounds with a cyclic dipeptide structure, which found widespread use and application in organic, medicinal, combinatorial and supramolecular chemistry. Thus, the piperazine-2,5-dione moiety is a constituent of natural products, such as dipodazine,[13] barettin,[14] tryptophane–dehydrobutyrine–diketopiperazine (TDD)[15] and (+)-tryprostatin.[16] Piperazine-2,5-diones also belong to a family of the 'privileged scaffolds', which are often used as key-building blocks in medicinal chemistry and in the synthesis of combinatorial libraries.[17] Due to their cyclic dipeptide structure with two amide units located at the opposite sides of the six-membered ring, they can readily assemble via intermolecular amide–amide C=*O*···*H*–N hydrogen bonds to form linear tape structures and the planar layer structures.[18–20] Finally, chiral non-racemic piperazine-2,5-dione derivatives are also important chiral auxiliaries, for example, in the asymmetric synthesis of enantiopure α-amino acids.[21]

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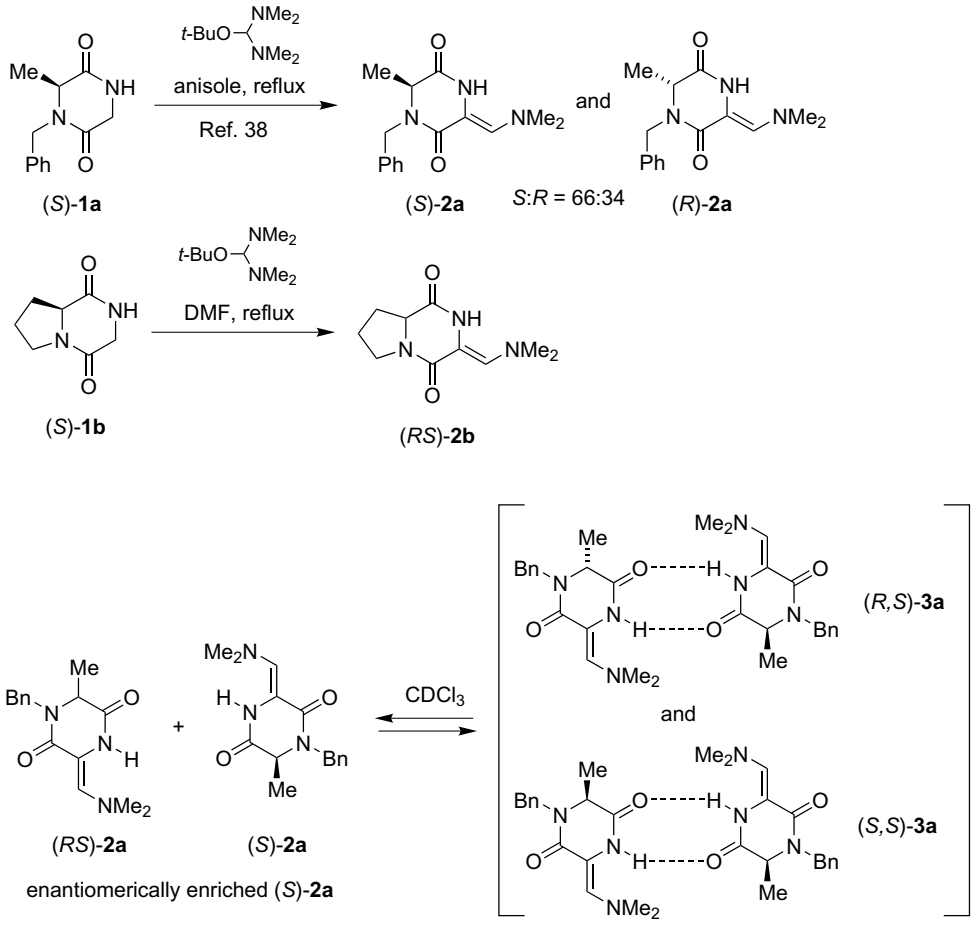
Over the course of our studies on the utilization of alkyl 2-(dimethylamino)propenoates and related enaminones in the synthesis of heterocyclic systems including functionalized heterocycles and natural product analogues,[22,23] we recently focused our attention also on preparation and synthetic applications of chiral non-racemic enaminones, available from α-amino acids[22,24–27] and (+)-camphor.[28–35] Within this context, we recently reported the enaminone-based preparation of chiral racemic dipodazine analogues.[27] Our initial intention to prepare the non-racemic dipodazine analogues failed, since transformation of the enantiopure (*S*)-1-benzyl-6-methylpiperazine-2,5-dione (*S*)-**1a** into the (*S*)-1-benzyl-3-[(*Z*)-(dimethylamino)methylidene]-6-methylpiperazine-2,5-dione (*S*)-**2a** was accompanied by partial racemization.[27] However, interesting behaviour of the intermediates, enantiopure (*S*)-**1a** and partially racemized (*S*)-**2a** in $CDCl_3$ solution, was observed by NMR during the development of the synthesis of dipodazine analogues. These observations prompted us to take a closer look at the structural features and behaviour of diketopiperazines **1a** and **2a** in solution. Herein, we report the results of this study, which showed that in $CDCl_3$ solution, enantiopure diketopiperazine (*S*)-**1a** readily forms diastereomeric hydrogen-bonded associates with chiral amides **2a**–**d**. This indicates that enantiopure diketopiperazines could serve as CSA for NMR determination of enantiomeric purity.

2. Results and discussion

Enantiopure diketopiperazines (*S*)-**1a** and (*S*)-**1b** were first prepared according to the literature procedures from commercially available (*S*)-alanine methyl ester hydrochloride[36–39] and (*S*)-proline methyl ester hydrochloride,[37–41] respectively. Treatment of compound (*S*)-**1a** with *tert*-butoxy-bis(dimethylamino)methane (TBDMAM, Bredereck's reagent) in refluxing anisole, according to the literature procedure, afforded partially racemized enamino piperazine (*S*)-**2a** in 75% yield and in 32% ee.[27] Later on, during repeated preparations, the 32% ee of (*S*)-**2a** was not reproducible and was usually lower than 20%. Similarly, heating of (*S*)-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (*S*)-**1b** with TBDMAM in anhydrous DMF for 3.5 h afforded racemic enamino piperazine (*RS*)-**2b** in 43% yield. Microwave irradiation shortened the reaction time to 15 min and eliminated the formation of coloured impurities, however, the yields of (*RS*)-**2b** and ee were not improved (Scheme 1).

The first interesting observation was made when the ^1H NMR spectrum of enantiomerically enriched enaminone (*S*)-**2a** in $CDCl_3$ at 23 °C was taken at approximately four times higher concentration (0.091 M) than the usual concentration (0.025 M) for taking routine ^1H NMR spectra. The spectrum of enantiomerically enriched (*S*)-**2a** at



Scheme 1.

higher concentration (0.091 M) exhibited two partially resolved singlets for the dimethylamino group in a ratio of 56:44. This was in contrast to the spectrum of enantiomerically enriched (*S*)-**2a** taken at lower concentration (0.025 M) and in contrast to the spectrum of the racemic compound (*RS*)-**2a** (0.025 M), both of which exhibited a singlet for the dimethylamino group (Fig. 1, spectrum A). This observation, as well as the known literature examples of self-induced NMR anisochrony of chiral, non-racemic α-amino acid derivatives,[42,43] led us to the conclusion that, in the $CDCl_3$ solution, enantiomerically enriched compound (*S*)-**2a** undergoes a reversible dimerization (association) via the N–*H*···*O*═C hydrogen bonds between the enantiomers (*S*)-**2a** and (*R*)-**2a**. Excess of the (*S*)-enantiomer induced NMR anisochrony exhibited as splitting of signals corresponding to diastereomeric dimers (*R*,*S*)-**3a** and (*S*,*S*)-**3a**. Thus, the enantiomeric excess of the (*S*)-isomer of enantiomerically enriched enaminone (*S*)-**2a** acted as a chiral solvating agent (CSA). On the other hand, in the racemic compound (*RS*)-**2a** the amounts of both enantiomers were identical and a fast exchange consequently led to averaging into a single signal for the dimethylamino group (Scheme 1).

We then considered that if the non-racemic compound (*S*)-**2a** underwent reversible association into (*R*,*S*)-**3a** and (*S*,*S*)-**3a**, then the singlet for the NMe_2 group in the racemic enaminones (*RS*)-**2a** and (*RS*)-**2b** should also be split in the presence of the enantiopure precursor, diketopiperazine (*S*)-**1a**. Indeed, ^{1}H NMR spectra of equimolar mixtures ($c = 0.092$ M) of (*RS*)-**2a**,**b** and the enantiopure (*S*)-**1a** in $CDCl_3$ at 23 °C exhibited two singlets for the NMe_2 group in a 1:1 ratio (Fig. 1, spectrum B). These spectra are in agreement with reversible formation of hydrogen-bonded diastereomeric associates (*R*,*S*)-**4a**,**b** and (*S*,*S*)-**4a**,**b** in $CDCl_3$ solution (Scheme 2).

Encouraged by these results, we focused our attention on the possible applications of (*S*)-**1a** as a chiral solvating agent in NMR spectroscopy. To do this, we needed a model cyclic amide, which was capable of interactions with (*S*)-**1a** via hydrogen bonding and that could be easily accessible in both enantiomeric forms. For this purpose, the (*R*)-, (*S*)- and (*RS*)-isomers of *tert*-butyl pyroglutamate **2c** were chosen and prepared from the corresponding commercially available isomers of pyroglutamic acid following the literature procedure.[44] The ^{1}H NMR spectrum of equimolar mixture ($c = 0.092$ M) of *tert*-butyl (*RS*)-pyroglutamate (*RS*)-**2c** and (*S*)-**1a** in $CDCl_3$ also exhibited two singlets for the *tert*-butyl group (Fig. 1, spectrum C), which were in agreement with formation of the diastereomeric associates (*R*,*S*)-**4c** and (*S*,*S*)-**4c** (Scheme 2).

Next, we used (*S*)-**1a** as a chiral solvating agent for the determination of the enantiomeric excess of the non-racemic *tert*-butyl pyroglutamate **2c** and evaluated the accuracy of the method. Known mixtures of enantiomers were weighed from the (*R*)-, (*S*)- and (*RS*)-isomer of **2c**. For each known isomeric mixture, the enantiomer composition was then re-determined by ^{1}H NMR in $CDCl_3$ in the presence of equimolar amounts of (*S*)-**1a**. All spectra were zero filled and gaussed prior to the processing. Ee was deter-

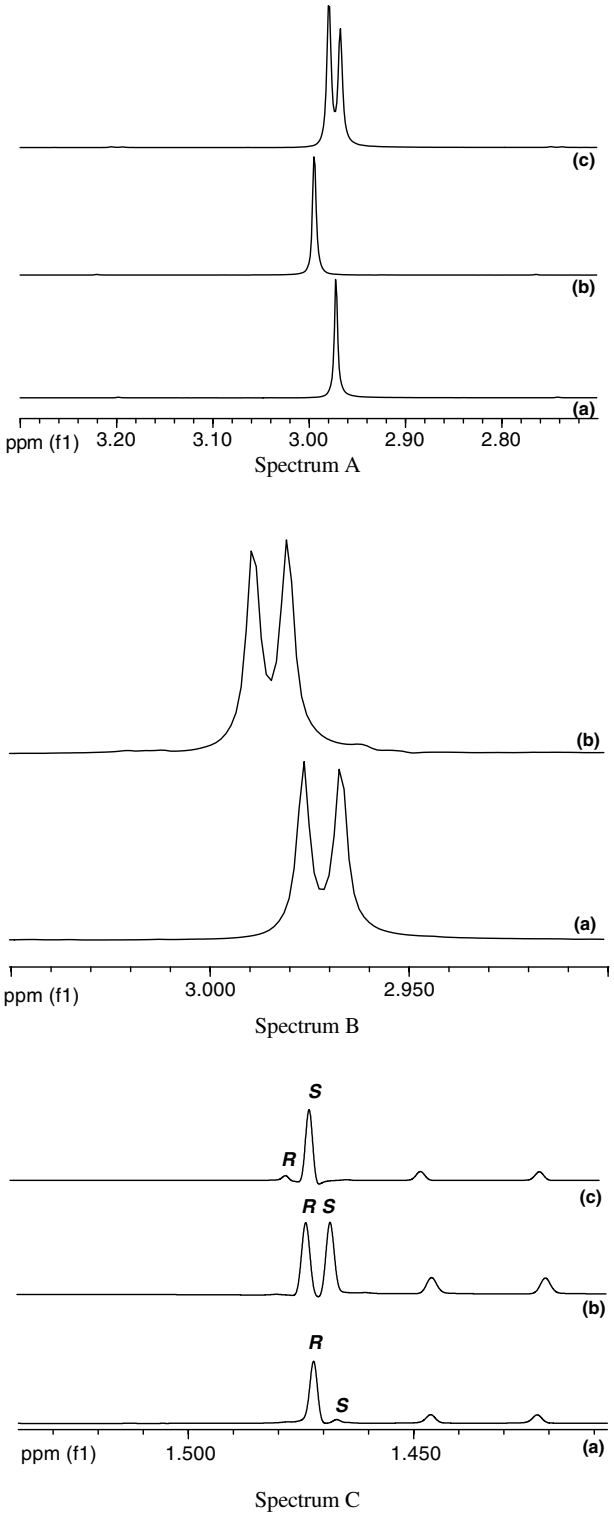
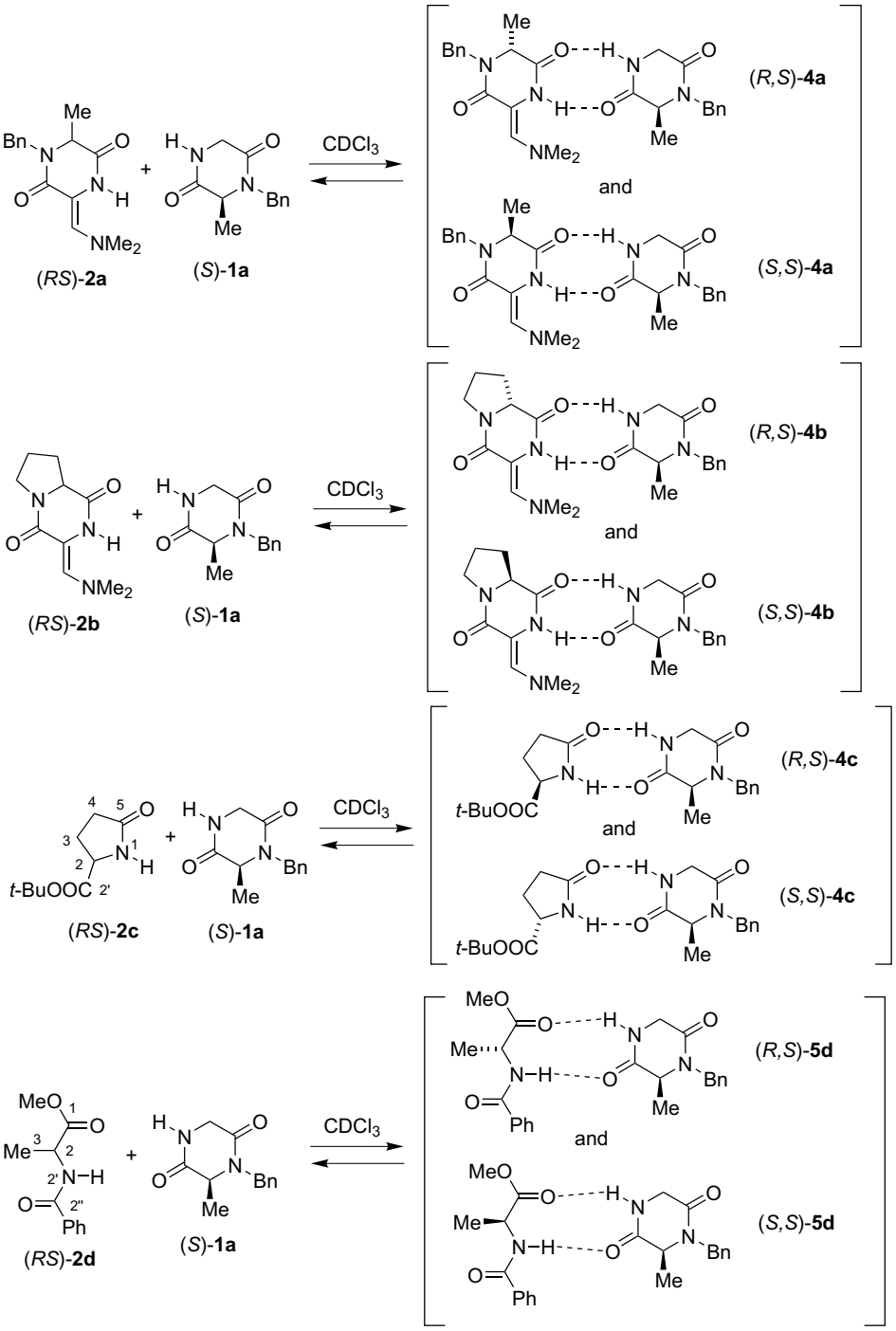


Figure 1. Spectrum A: signal for the NMe_2 group in partial ^{1}H NMR spectrum (300 MHz) of (a) racemic (*RS*)-**2a** (0.025 M), (b) enantiomerically enriched (*S*)-**2a** (0.025 M) and (c) enantiomerically enriched (*S*)-**2a** (0.091 M) in $CDCl_3$. Spectrum B: signal for the NMe_2 group in partial ^{1}H NMR spectrum (300 MHz) of (a) (*RS*)-**2a** in the presence of 1 equiv of (*S*)-**1a** (0.092 M), (b) (*RS*)-**2b** in the presence of 1 equiv of (*S*)-**1a** (0.092 M) in $CDCl_3$. Spectrum C: signal for the *tert*-butyl group in partial ^{1}H NMR spectrum (300 MHz) of (a) (*R*)-**2c** (90.9% ee), (b) (*RS*)-**2c** and (c) (*S*)-**2c** (90.9% ee) in $CDCl_3$. Ee was determined from the relative intensities of signals of the *tert*-butyl group.



Scheme 2.

Table 1. Theoretical and experimental ee values and relative errors (E_r) in determination of enantiomer composition of compound **2c** using (*S*)-**1a** as a chiral solvating agent

Method	Enantiomer composition						
	(*S*)-Enriched			←(*RS*)→		(*R*)-Enriched	
ee (%) by weight	90.87	61.86	22.81	0	21.86	59.36	90.94
ee (%) by NMR[a]	88.68	57.48	19.05	0	20.48	56.25	88.68
E_r (%)	−2.41	−7.08	−16.48	0	−6.31	−5.24	−2.49
E_r Mean (%)				−5.72			

[a] All spectra were taken in $CDCl_3$ at 23 °C.

mined from the relative intensities of signals of the *tert*-butyl group (cf. Fig. 1, spectrum C). The results are summarized in Table 1. Linear regression and relative error were determined in order to evaluate the experimental data. To our delight, both Pearson's coefficient of correlation ($R^2 = 0.9994$) and relative error ($E_r = -5.72\%$) were in agreement with the theoretical (weighed) ee values, thus showing the good accuracy of (*S*)-**1a** as a CSA (Fig. 2, Table 1).

Once the applicability of (*S*)-**1a** as a chiral solvating agent for racemic lactams **2a**–**c** was confirmed, we attempted to see if (*S*)-**1a** could be used as CSA in the case of non-cyclic racemic amides, such as (*RS*)-*N*-benzoylalanine methyl ester (*RS*)-**2d**.[45] Thus, the ^{1}H NMR spectra of an equimolar mixture of (*S*)-**1a** and (*RS*)-**2d** were taken in $CDCl_3$ at 25, −15 and −40 °C. At room temperature, the signal for the NH proton of (*RS*)-**2d** appeared as two partially resolved doublets, whilst complete resolution was achieved at −15 °C. At −40 °C the resolution was even better, however, the left doublet of resolved NH signals of (*RS*)-**2d** was overlapped by the aromatic protons due to an additional downfield shift of the NH signals (Fig. 3). This supported formation of the diastereomeric associates, such as (*R*,*S*)-**5d** and (*S*,*S*)-**5d** (Scheme 2).

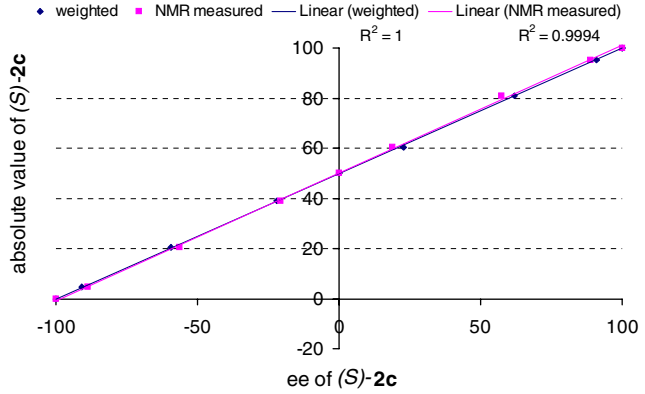


Figure 2. Linear regression and Pearson's coefficient of correlation ($R^2 = 0.9994$) in the ^{1}H NMR determination of ee of (*R*)-**2c** or (*S*)-**2c** using (*S*)-**1a** as a chiral shift reagent. Weighed values and linear are depicted in blue. Experimental NMR values and linear are depicted in purple.

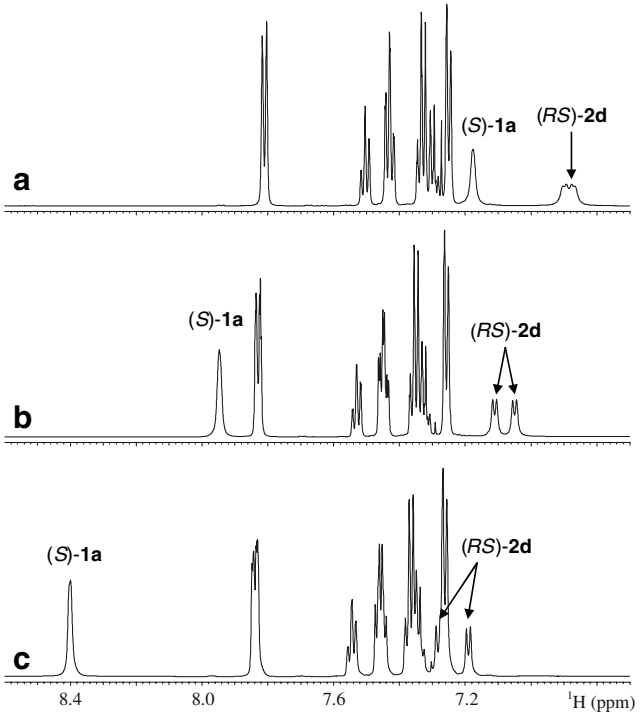


Figure 3. Signals for the NH protons of (*RS*)-**2d** and (*S*)-**1a** in partial ^{1}H NMR spectrum (600 MHz) of equimolar mixture of (*RS*)-**2d** and (*S*)-**1a** in $CDCl_3$ at (a) 25 °C, (b) −15 °C and (c) −40 °C.

3. Structural study

First, the interactions of (*RS*)-**2a**,**b** with (*S*)-**1a** in solution were studied by NMR. The spectra of mixtures of (*RS*)-**2a**,**b** and (*S*)-**1a** were recorded at different concentrations (0.025–0.11 M) in DMSO-d_6 and in $CDCl_3$ as solvents. In DMSO-d_6, single sets of signals for (*RS*)-**2a**,**b** were observed, regardless of the concentration of the sample. This was not very surprising, since DMSO-d_6 as a hydrogen bond acceptor minimizes interactions between (*RS*)-**2**,**b** and (*S*)-**1a**. On the other hand, $CDCl_3$ does not form hydrogen bonds and interactions between (*RS*)-**2a**,**b** and (*S*)-**1a** are feasible. The resolution of signal splitting increased with increasing concentration of the sample. Well resolved signals were obtained at concentrations above 0.07 M. This concentration dependence was in agreement with the assumed reversible formation of diastereomeric associates (*SS*)-**4a**,**b** (*RS*)-**4a**,**b** in $CDCl_3$ solution. The existence of (*SS*)-**4a**,**b** (*RS*)-**4a**,**b** in $CDCl_3$ was unambiguously established by 2D NMR spectroscopy on the basis of intermolecular NOE (Fig. 4).[46–51] Chemical exchange signals between the split signals of NH protons of (*RS*)-**2a** and (*RS*)-**2b** were observed in the ROESY and the NOESY spectra, which confirmed the existence of two exchanging isomers of (*RS*)-**2a** and (*RS*)-**2b** in the mixture with (*S*)-**1a**. At −15 °C, the exchange rate was sufficiently reduced and each isomer of (*RS*)-**2a** or (*RS*)-**2b** had individual NOE cross-peaks (Fig. 5).

tert-Butyl pyroglutamate **2c** possesses two hydrogen bond acceptors, the ester carbonyl group and the amide carbonyl group. Consequently, the mode of binding of (*S*)-**1a** to **2c** in $CDCl_3$ solution could not be the same as in the case of associates **4a**,**b** (cf. Scheme 2). We wanted to determine, which of the two carbonyl groups of **2c** is actually involved in hydrogen bonding with (*S*)-**1a**. The first indication came from the comparison of the ^{13}C NMR spectra of (a) pure (*S*)-**2c** and (b) a mixture of (*S*)-**2c** and (*S*)-**1a**. Namely, the presence of (*S*)-**1a** caused a small shift $\Delta\delta$ of all carbon nuclei of (*S*)-**2c**. However, the shift of the lactam carbonyl group ($\Delta\delta = +0.61$ ppm) was much larger than the shift of the ester carbonyl group ($\Delta\delta = +0.08$ ppm) and the 2-*C*, 3-*C*, 4-*C* and Me_3C carbon nuclei ($\Delta\delta \sim \pm 0.1$ ppm). This supported the premise that in compound **2c**, the amidic carbonyl group acts as a H-bond acceptor (Table 2). Determination of the binding mode was then done by 2D NMR spectroscopy on the basis of intermolecular NOE between

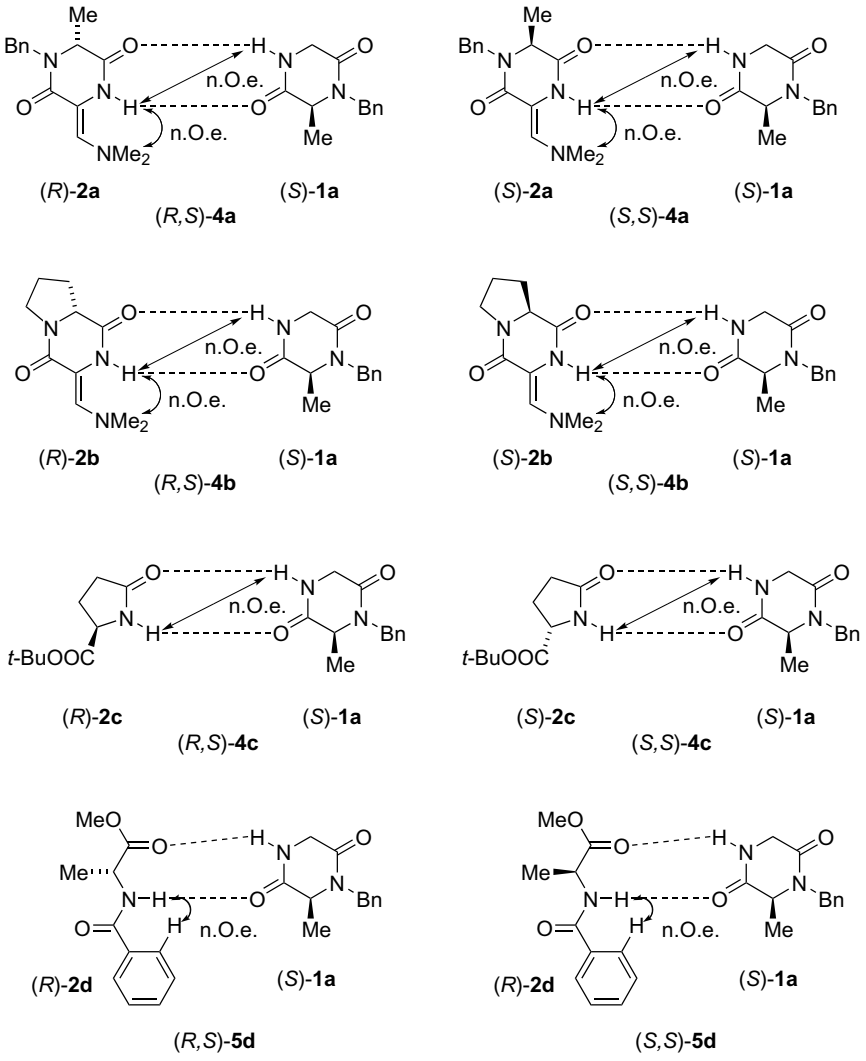


Figure 4. Determination of the structures of associates **4a**–**c** and **5d** between racemic (*RS*)-**2a**–**d** and enantiopure (*S*)-**1a** using the intermolecular NOEs in $CDCl_3$ at −15 °C.

the NH protons in the same manner as already described above for associates **4a**,**b** (Figs. 4 and 5).

Similarly, *N*-benzoylalanine ester **2d** as acyclic analogue also contains two possible hydrogen bond acceptors: the amide and the ester carbonyl group. However, in contrast to *tert*-butyl pyroglutamate (**2c**), acyclic amide **2d** can adopt a more favourable *trans*-conformation around the C–N amide bond. 2D ROESY spectrum of a mixture of (*S*)-**1a** and (*RS*)-**2d** in $CDCl_3$ at −15 °C revealed a strong NOE between the NH of (*RS*)-**2d** and the *ortho*-protons in the *N*-benzoyl group, while no intermolecular NOE between the NH protons of (*S*)-**1a** and (*RS*)-**2d** was observed (Figs. 4 and 5). However, a strong downfield shift of both NH protons ($\Delta\delta = +0.66$ ppm for (*S*)-**1a** and +0.36 ppm for (*RS*)-**2d**, cf. Fig. 3) was in agreement with the presumption that double hydrogen-bonded associates (*RS*)-**5d** and (*SS*)-**5d** are formed in $CDCl_3$ solution of a mixture of (*S*)-**1a** and (*RS*)-**2d** (cf. Scheme 2). Furthermore, the ^{13}C NMR spectrum of a mixture of (*S*)-**1a** and (*RS*)-**2d** exhibited the splitting of signals for the ester *C*=O group and the 3-CH_3 group of compound (*RS*)-**2d**. The downfield shift of the ester carbon ($\Delta\delta = +0.13$ ppm) and the upfield shift of the amide carbon ($\Delta\delta = -0.15$ ppm) supported the premise that the ester group C=O is involved in hydrogen bonding, while the amide C=O group is not (Table 3). On the other hand, the absence of inermolecular NOE can be explained by the higher conformational flexibility of the proposed associates **5** in comparison to more rigid associates **4** (Fig. 4).

In addition to the X-ray structure of the enamino lactam (*RS*)-**2a**,[27] the structures of compounds (*S*)-**1a** and (*S*)-**2c** were also determined by X-ray diffraction. X-ray data for single crystals of (*S*)-**1a**, (*RS*)-**2a** and (*S*)-**2c** were compared with the structural data for associates **4a**–**c** obtained by NMR spectroscopy. The crystal structure of diketopiperazine (*RS*)-**2a**[27] (Fig. 6) was comparable to associates **4a** and **4b** formed in solution, since dimeric, double hydrogen-bonded structures were established in both cases. The N–O distance in the crystalline (*RS*)-**2a** is 2.887(3) Å (both H-bonds are symmetrically equivalent). On the other hand,

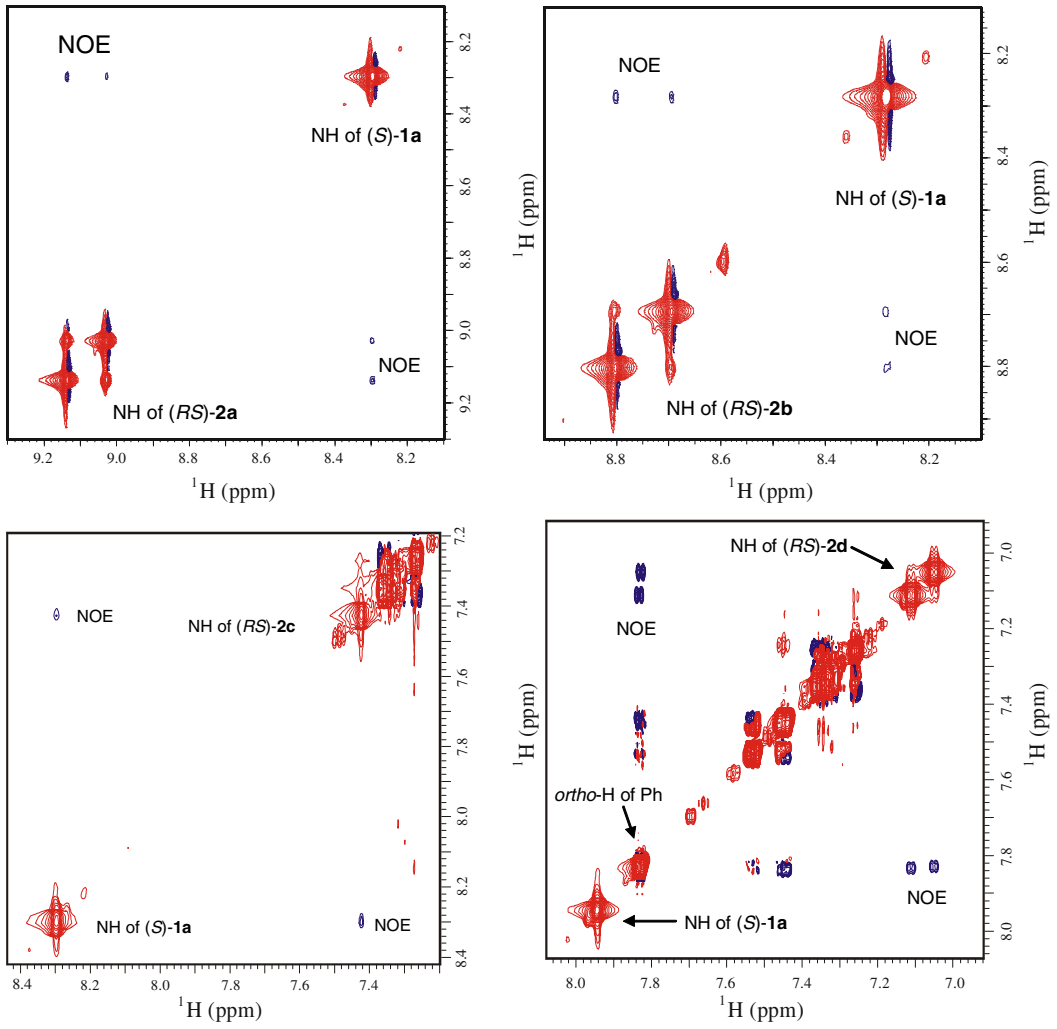


Figure 5. Partial ROESY spectra (600 MHz) of mixtures of (*RS*)-**2a–d** and (*S*)-**1a** in $CDCl_3$ at −15 °C.

Table 2. ^{13}C NMR data for compound (*S*)-**2c** and a mixture of (*S*)-**2c** and (*S*)-**1a**[a]

	δ (ppm)		Δδ (ppm)
	(*S*)-**2c**[b]	(*S*)-**2c**[c] + (*S*)-**1a**[c]	
(5)*C*=O (Amide)	177.47	178.08	+0.61
(2′)*C*=O (Ester)	170.98	171.06	+0.08
(2)*C*–H	55.93	56.10	+0.17
(3)CH_2	24.87	24.78	−0.09
(4)CH_2	29.27	29.37	+0.10
CMe_3	82.45	82.27	−0.18
Me_3C	27.97	27.91	−0.06

[a] Both spectra were taken in $CDCl_3$ at 23 °C.
[b] $c = 0.034$ M.
[c] $c = 0.092$ M.

Table 3. ^{13}C NMR data for compound (*S*)-**2d** and a mixture of (*S*)-**2d** and (*S*)-**1a**[a]

	δ (ppm)		Δδ (ppm)
	(*RS*)-**2d**[b]	(*RS*)-**2d**[c] + (*S*)-**1a**[c]	
(1)*C*=O (Ester)	173.68	173.79[d]	+0.11[d]
		173.84[d]	+0.16[d]
(2″)*C*=O (Amide)	166.76	166.91	−0.15
C–Ar	133.97	133.89	+0.08
C–Ar	131.73	131.73	−0.00
C–Ar	128.59	128.56	+0.03
C–Ar	127.03	127.09	−0.06
OCH_3	52.58	52.58	−0.00
2-*C*	48.50	48.49	+0.01
(3)CH_3	18.72	18.51[d]	+0.21[d]
		18.53[d]	+0.20[d]

[a] Both spectra were taken in $CDCl_3$ at 25 °C.
[b] $c = 0.027$ M.
[c] $c = 0.090$ M.
[d] Resolved signals for (*R*,*S*)-**5d** and (*S*,*S*)-**5d**.

X-ray diffraction analysis of the other diketopiperazine (*S*)-**1a** and *tert*-butyl (*S*)-pyroglutamate [(*S*)-**2c**] established zig-zag crystal structures, where each molecule binds with two other molecules via the amidic N–H···O=C(5) symmetrically equivalent hydrogen bonds (Figs. 7 and 8). The N–O distances in these cases are 2.834(3) and 2.914(3) Å for (*S*)-**1a** and (*S*)-**2c**, respectively. This was in contrast to the formation of dimeric associates **4c** in $CDCl_3$

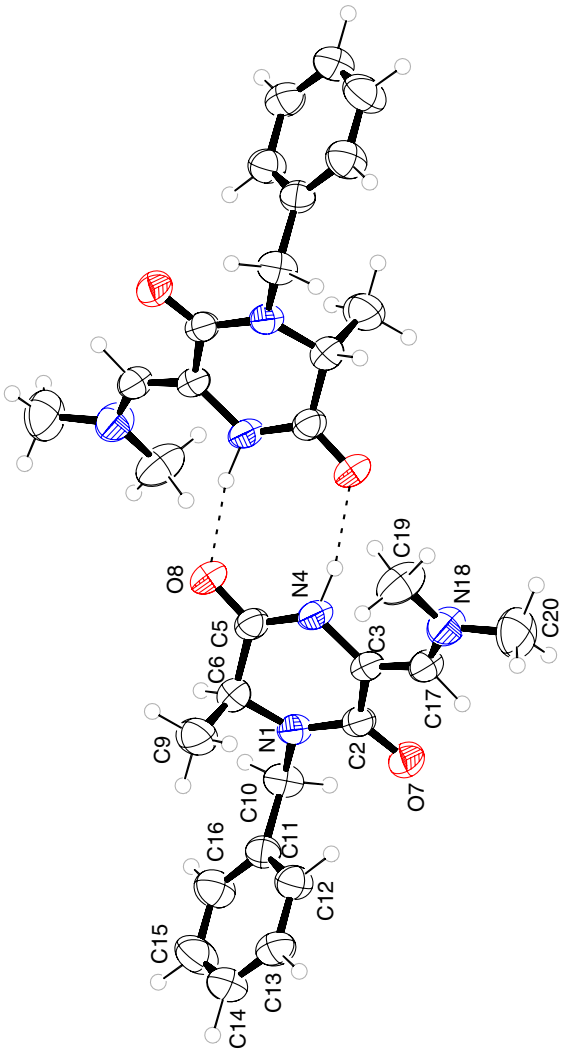


Figure 6. ORTEP plot of the dimeric unit of (*RS*)-**2a** in the crystal structure. Ellipsoids are plotted at 50% probability, hydrogen bonds are depicted as dashed lines, atom labelling of one asymmetric unit is shown.

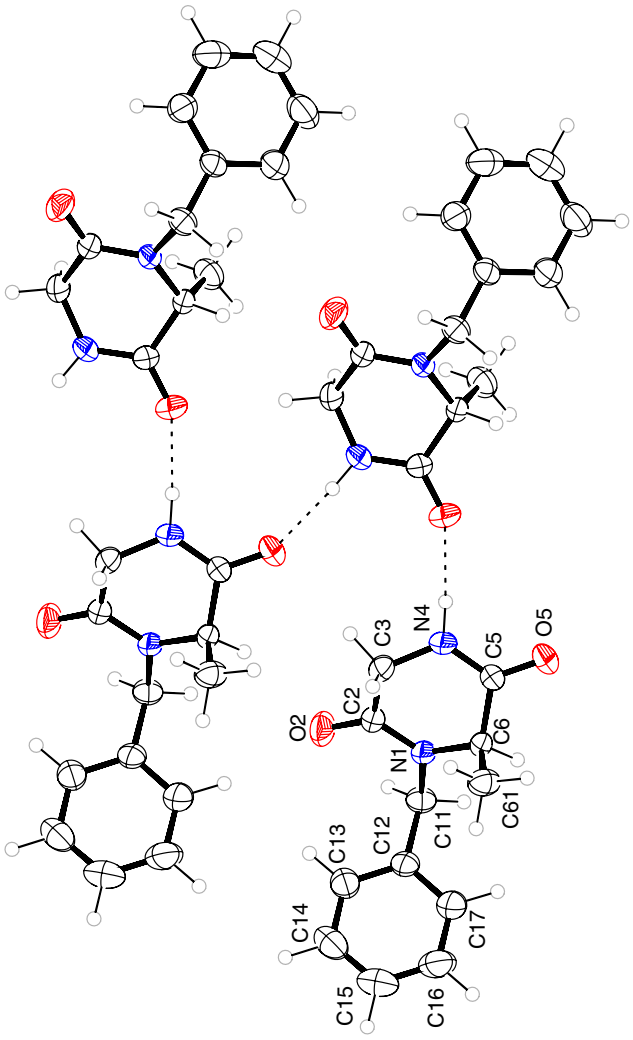


Figure 7. ORTEP plot of the zig-zag chain of (*S*)-**1a** in the crystal structure. Ellipsoids are plotted at 50% probability, hydrogen bonds are depicted as dashed lines, atom labelling of one asymmetric unit is shown.

solution (cf. Scheme 2). Unfortunately, and despite several attempts, we were unable to prepare single crystals of any of the associates **4a**–**c**.

Besides the binding mode, we were also interested in the affinity of association of **2a**–**c** with **1a**. This was estimated on the basis of $\Delta\delta$ chemical shifts for the NH in compounds **2a**–**c**. In combination with **1a**, all amidic protons of (*RS*)-**2a**–**c** were shifted to a lower magnetic field ($\Delta\delta = 1.50$–1.70 ppm). Chemical shifts of amidic protons of **2a**–**c**, alone and in combination with (*S*)-**1a**, are summarized in Table 4. We believe that these data indicate the following affinity of association: **4a** $\geqslant$ **4b** $\geqslant$ **4c**.

4. Conclusion

In $CDCl_3$ solution, the enantiopure (*S*)-1-benzyl-6-methylpiperazine-2,5-dione (*S*)-**1a** undergoes reversible formation of diastereomeric hydrogen-bonded associates (*R**,*S*)-**4a**–**c** and (*R**,*S*)-**5d** with racemic amides (*RS*)-**2a**–**c** and (*RS*)-**2d**, respectively. This reversible association results in induced NMR anisochrony and splitting of characteristic signals of (*RS*)-**2a**–**d**. The existence and structure of diastereomeric associates **4a**–**c** and **5d** were studied by NMR methods. The structures of **4a**–**c** were unambigously determined on the basis of intermolecular NOE between the amidic protons of (*S*)-**1a** and (*RS*)-**2a**–**c**. The structure of **5d** was proposed on the basis of the chemical shifts of NH protons and carbon nuclei of C=O groups. Diketopiperazine (*S*)-**1a** was then used as a chiral solvating agent for the determination of ee of the non-racemic *tert*-butyl pyroglutamate **2c**. The good accuracy of the method was established, since the experimental ee values were in agreement with theoretical values. Thus, (*S*)-**1a** is a simple and easily available enantiopure compound, which can be used as a chiral solvating agent for the determination of the ee of non-racemic chiral amides by ^{1}H NMR. Another advantage of (*S*)-**1a** in comparison with lanthanide-based chiral shift reagents is the absence of a paramagnetic lanthanide nuclei, that is, the resolution of ^{1}H NMR spectra

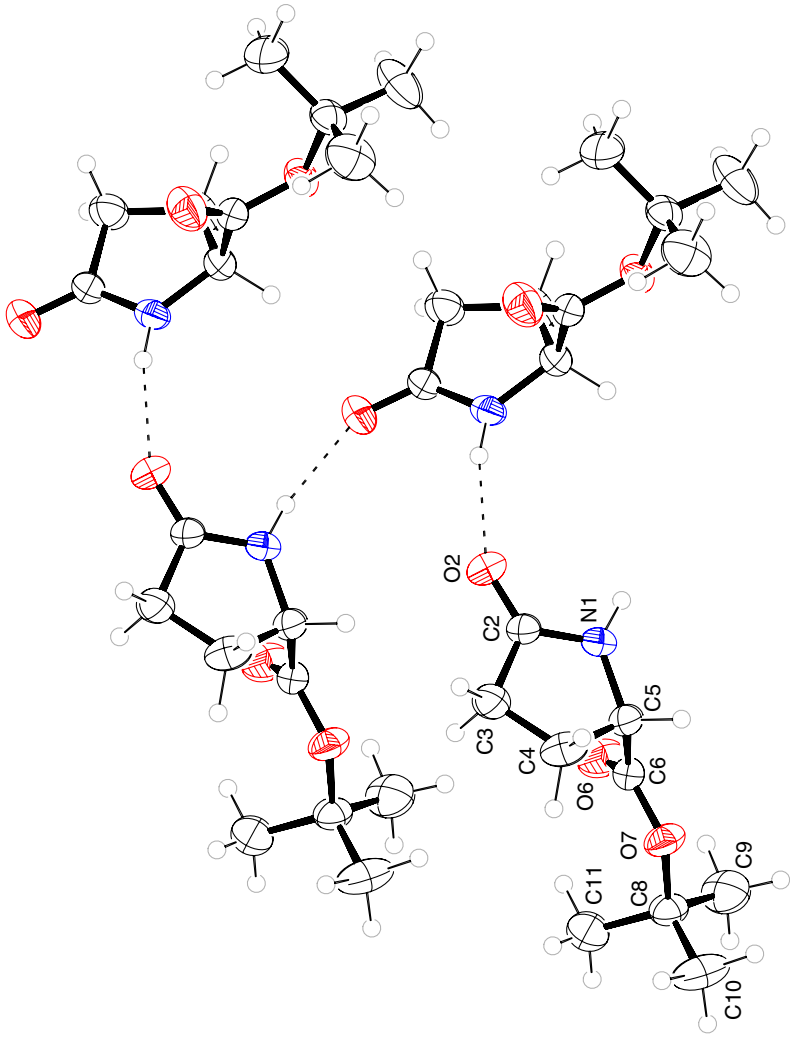


Figure 8. ORTEP plot of the zig-zag chain of (*S*)-**2c** in the crystal structure. Ellipsoids are plotted at 50% probability, hydrogen bonds are depicted as dashed lines, atom labelling of one asymmetric unit is shown.

Table 4. Chemical shifts of NH protons in compounds **2a**–**c** in the presence of (*S*)-**1a**[a]

Compound	c (mol L^{-1})	T (°C)	δ (ppm)	$\Delta\delta$ (ppm)
(*RS*)-**2a**	0.022	23	7.44	
(*RS*)-**2a** + (*S*)-**1a**	0.092	−15	9.03/9.14[b]	1.59/1.70[b]
(*RS*)-**2b**	0.030	23	7.21	
(*RS*)-**2b** + (*S*)-**1a**	0.092	−15	8.71/8.82[b]	1.50/1.61[b]
(*RS*)-**2c**	0.034	23	5.94	
(*RS*)-**2c** + (*S*)-**1a**	0.092	−15	7.43	1.49

[a] All spectra were taken in $CDCl_3$.
[b] Resolved NH signals for (*R*,*S*)-**4a**,**b** and (*S*,*S*)-**4a**,**b**.

of the compounds investigated (*RS*)-**2a**–**d** was retained upon addition of (*S*)-**1a**, whilst the use of commercially available lanthanide-based chiral shift reagents is often accompanied by substantially diminished resolution of ^{1}H NMR spectra. Further study on the preparation and utilization of novel diketopiperazine-based CSA is currently in progress.

5. Experimental

5.1. General methods

Melting points were determined on a Kofler micro hot stage. The 1D NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. The 2D NMR spectra were taken on a Varian INOVA 600 MHz and on a Varian DirectDrive 600 MHz spectrometer. Optical rotations were measured on a Perkin–Elmer 241MC Polarimeter. Mass spectra were recorded on an AutoSpecQ spectrometer and IR spectra on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyzer 2400 II.

tert-Butoxy-bis(dimethylamino)methane, (*S*)-alanine methyl ester hydrochloride and (*S*)-proline methyl ester hydrochloride are commercially available (Sigma–Aldrich). (*S*)-1-Benzyl-6-methylpiperazine-2,5-dione (*S*)-**1a** and

(*S*)-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (*S*)-**1b**,[36–41] (*S*)-1-benzyl-3-[(*Z*)-(dimethylamino)methylidene]-6-methylpiperazine-2,5-dione (*S*)-**2a**,[27] (*R*)-, (*S*)- and (*RS*)-isomer of *tert*-butyl pyroglutamate **2c**[44] and (*RS*)-*N*-benzoylalanine methyl ester (*RS*)-**2d**[45] were prepared according to the literature procedures.

Source of chirality: (i) L-alanine methyl ester hydrochloride (Fluka AG), product number 05200, puriss., ⩾99.0% (dried material AT), $[\alpha]_D^{20} = +7.5 \pm 0.5$ (*c* 2, MeOH), mp 107–110 °C, ee not specified; (ii) D-pyroglutamic acid (Fluka AG), product number 83165, puriss., ⩾99.0% (T), $[\alpha]_D^{20} = +10.5 \pm 1$ (*c* 5, H_2O), mp 155–162 °C, ee ⩾98.0% (GC); (iii) L-pyroglutamic acid (Fluka AG), product number 83160, puriss., ⩾99.0% (T), $[\alpha]_D^{20} = -10.5 \pm 1$ (*c* 5, H_2O), mp 155–162 °C, ee ⩾98.0% (GC).

5.2. (*S*)-1-Benzyl-6-methylpiperazine-1,4-dione (*S*)-1a

This compound was prepared from (*S*)-alanine methyl ester hydrochloride following the literature procedures via reductive benzylation,[36] chloroacetylation[37] and cyclization.[37–39] Mp 176–178 °C (from MeOH); lit.[37] mp not given. $[\alpha]_D^{20} = +37.5$ (*c* 2.90, $CHCl_3$); lit.[37] $[\alpha]_D^{20} = +37.5$ (*c* 2.85, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, $c = 0.033$ M): δ 1.32 (3H, d, $^3J = 7.2$ Hz, CH_3); 3.68 (1H, q, $^3J = 7.2$ Hz, 6-H); 3.71 (1H, dd, $^2J = 17.3$ Hz, $^3J = 3.2$ Hz, 1H of CH_2NH); 4.10 (1H, d, $^2J = 17.3$ Hz, 1H of CH_2NH); 4.18 (1H, d, $^2J = 15.1$ Hz, 1H of CH_2Ph); 4.92 (1H, d, $^2J = 15.1$ Hz, 1H of CH_2Ph); 7.30–7.40 (5H, m, Ph); 8.13 (1H, br d, $^3J = 3.0$ Hz, CH_2NH). ^{1}H NMR (300 MHz, $CDCl_3$, $c = 0.033$ M): δ 1.44 (3H, d, $^3J = 7.1$ Hz, CH_3); 3.68 (1H, q, $^3J = 7.1$ Hz, 6-H); 4.02 (1H, dd, $^2J = 17.3$ Hz, $^3J = 3.8$ Hz, 1H of CH_2NH); 4.07 (1H, d, $^2J = 15.1$ Hz, 1H of CH_2Ph); 4.11 (1H, d, $^2J = 17.3$ Hz, 1H of CH_2NH); 5.20 (1H, d, $^2J = 15.1$ Hz, 1H of CH_2Ph); 6.52 (1H, br s, CH_2NH); 7.20–7.40 (5H, m, Ph). ^{1}H NMR (300 MHz, $CDCl_3$, $c = 0.275$ M): δ 1.42 (3H, d, $^3J = 7.1$ Hz, CH_3); 3.82 (1H, q, $^3J = 7.1$ Hz, 6-H); 3.99 (1H, dd, $^2J = 17.3$ Hz, $^3J = 3.8$ Hz, 1H of CH_2NH); 4.06 (1H, d, $^2J = 15.1$ Hz, 1H of CH_2Ph); 4.07 (1H, d, $^2J = 17.3$ Hz, 1H of CH_2NH); 5.19 (1H, d, $^2J = 15.1$ Hz, 1H of CH_2Ph); 7.20–7.39 (5H, m, Ph); 7.56 (1H, br s, CH_2NH). ^{13}C NMR (75.5 MHz, $CDCl_3$, $c = 0.033$ M): δ 17.48; 44.94; 47.33; 55.10; 128.08; 128.21; 128.94; 135.55; 163.89; 169.64. ^{13}C NMR (75.5 MHz, $CDCl_3$, $c = 0.275$ M): δ 17.35; 44.72; 47.20; 55.05; 127.97, 128.10; 128.84; 135.51; 164.04; 170.11. *m/z* (EI) = 218 (M^+). *m/z* (HRMS) found: 218.104185 (M^+). $C_{12}H_{14}N_2O_2$ requires: *m/z* = 218.105700. (Found: C, 66.15; H, 6.69; N, 12.56. $C_{12}H_{14}N_2O_2$ requires: C, 66.04; H, 6.47; N, 12.84.); ν_{max} (KBr) 3240, 1698 (C=O), 1655 (C=O), 1433, 1322, 1123, 1064, 987, 787, 722, 704 cm^{-1}.

5.3. Preparation of (8a*RS*,3*Z*)-3-[(dimethylamino)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (*RS*)-2b

5.3.1. Procedure A. Bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent, 1.36 mL, 6.5 mmol) was added to a solution of (*S*)-**1b** (0.77 g, 5 mmol) in anhydrous DMF (6 mL) and the mixture was stirred at reflux for 3.5 h. The reaction mixture was cooled, the volatile components were evaporated in vacuo and the solid residue was crystallized from toluene to give (*RS*)-**2b**.

5.3.2. Procedure B. Bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent, 1.36 mL, 6.5 mmol) was added to a solution of (*S*)-**1b** (0.77 g, 5 mmol) in anhydrous DMF (6 mL) and the mixture was stirred in a closed vessel under microwave irradiation (T = 153 °C) for 15 min. The reaction mixture was cooled, then volatile components were evaporated in vacuo and the solid residue was crystallized from toluene. The precipitate was collected by filtration to give (*RS*)-**2b**.

Yield: 0.448 g (43%) of pale yellow crystals; mp 199–202 °C. ^{1}H NMR (300 MHz, $CDCl_3$, $c = 0.030$ M): δ 1.80–2.20 and 2.25–2.40 (4H, 2m, 3:1, 7-CH_2 and 8-CH_2); 2.98 (6H, s, NMe_2); 3.50–3.70 (2H, m, 6-CH_2); 4.00–4.10 (1H, m, 8a-H); 6.67 (1H, s, 3′-H); 7.21 (1H, br s, NH). ^{1}H NMR (300 MHz, DMSO-d_6, $c = 0.030$ M): δ 1.71–1.98 and 2.00–2.15 (4H, 2m, 3:1, 7-CH_2 and 8-CH_2); 2.90 (6H, s, NMe_2); 3.30–3.39 (2H, m, 6-CH_2); 3.93–4.01 (1H, m, 8a-H); 6.47 (1H, s, 3′-H); 9.16 (1H, br s, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$, $c = 0.040$ M): δ 22.32, 28.13; 42.72; 45.06; 58.37; 103.18; 132.53; 161.88; 165.89. *m/z* (EI) = 209 (M^+). *m/z* (HRMS) found: 209.116950 (M^+). $C_{10}H_{15}N_3O_2$ requires: *m/z* = 209.116427. (Found: C, 57.19; H, 7.35; N, 19.82. $C_{10}H_{15}N_3O_2$ requires: C, 57.40; H, 7.23; N, 20.08.); ν_{max} (KBr) 3446, 3008, 2989, 2926, 1687, 1667, 1578, 1358, 1115, 1101, 906, 739 cm^{-1}.

5.4. 2D NMR methods

The samples were prepared in 0.7 mL of dried $CDCl_3$ in a nitrogen atmosphere. The spectra were recorded in a phase sensitive mode at −15 °C. ROESY[52] and NOESY[53] spectra were acquired with 4096 data points in the t_2 dimension, 32 scans, 314–436 complex points in the t_1 dimension, a mixing time of 300 ms and a relaxation delay of 2 s. The spin-lock field of 3 kHz was used in the ROESY experiment. The DQF-COSY[54] spectra were recorded with 4096 data points in the t_2 dimension, 4 scans, 512 complex points in the t_1 dimension and a relaxation delay of 1.5 s. ^{1}H sweep widths were 6060, 6060, 5980 and 5914 Hz for mixtures of (*S*)-**1a** with (*RS*)-**2a**, (*RS*)-**2b**, (*RS*)-**2c** and (*RS*)-**2d**, respectively. The spectra were zero-filled two times and apodized with a squared sine bell function shifted by π/2 in both dimensions.

5.5. X-ray structure analysis for compounds (*S*)-1a and (*S*)-2c

Single crystal X-ray diffraction data of compounds (*S*)-**1a** and (*S*)-**2c** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[55] DENZO and SCALEPACK[56] were used for indexing and scaling of the data. The structures were solved by means of SIR97.[57] Refinement was carried out using Xtal3.4[58] program package and the crystallographic plots were prepared by ORTEP III.[59] Crystal structures were refined on *F* values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically in all cases. The positions of hydrogen atoms

were geometrically calculated and their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. Regina[60] weighting scheme was used in all cases.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 631733 and 631734. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033] or e-mail: deposit@ccdc.cam.ac.uk.

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