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Enantiomers of all-*cis*-5-(4-bromophenyl)-4-*tert*-butoxycarbonyl-2-methoxycarbonylpyrrolidine: preparative HPLC separation and acylative kinetic resolution of the racemate

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ABSTRACT

The fundamental possibility of acylative kinetic resolution of racemic heterocyclic amines was demonstrated by the example of all-*cis*-5-(4-bromophenyl)-4-*tert*-butoxycarbonyl-2-methoxycarbonylpyrrolidine. Individual enantiomers (*ee* >99%) were obtained in high yields via preparative chiral HPLC.

1. Introduction

Enantiopure derivatives of 5-arylpyrrolidine-2,4-dicarboxylic acid **1** represent a valuable compound class for different medicinal chemistry projects. The parent molecular scaffold **1** comprises of a conformationally rigid five-membered framework and three stereogenic centres that dispose the substituents and functional groups in a well-defined manner (Fig. 1). The secondary amine group and two carboxylic functions of **1** provide an excellent possibility for subsequent molecular diversity generation. Modification of the (2*S*,4*S*,5*R*)-analogue of **1** (Ar = Ph) with (*S*)-3-mercapto-2-methylpropanoyl residue led to a potent (K_i 160 pM) angiotensin converting enzyme (ACE) inhibitor **2**.[1] The diastereoisomer of **2** with a (2*R*,4*R*,5*S*)-configuration of the pyrrolidine ring displayed very weak ACE-inhibitory activity (K_i >1 μM). (2*S*,4*S*,5*R*)-*N*-Benzoyl 2,4-diacid **3** was identified as a sub-micromolar (IC_{50} 190 nM) inhibitor of an RNA-dependent RNA polymerase activity of the hepatitis C virus (HCV).[2] The opposite (2*R*,4*R*,5*S*)-isomer of **3** was two orders less effective. Subsequent optimization of compound (2*S*,4*S*,5*R*)-**3** led to the clinical development candidate of an anti-HCV agent with the same absolute configuration of the pyrrolidine scaffold.[3] Recently, non-basic racemic thrombin inhibitors

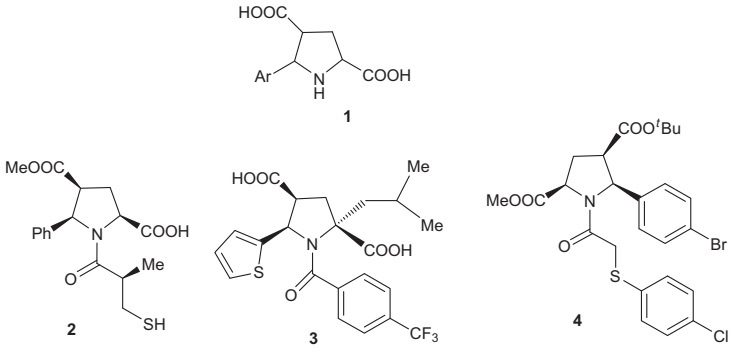

Figure 1. Biologically active derivatives of 5-arylpyrrolidine-2,4-dicarboxylic acid **1**.

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that contain a 5-arylpyrrolidine-2,4-dicarboxylic acid fragment were reported.[4] Molecular modelling has differentiated binding modes and energies of enantiomeric inhibitors and predicted some favourable interactions of the (2*R*,4*R*,5*S*)-ligand **4** set with the enzyme active site.[4]

Enantiomerically pure orthogonally protected diesters of 5-arylpyrrolidine-2,4-dicarboxylic acid **1** can generally be efficiently synthesized by the asymmetric 1,3-dipolar cycloaddition of acrylates to azomethine ylides.[5] The resolution of racemic derivatives of **1** via diastereoisomeric salt formation has been used in a few cases.[6] However, the preparation of enantiopure derivatives of 5-arylpyrrolidine-2,4-dicarboxylic acid remains an important synthetic challenge.

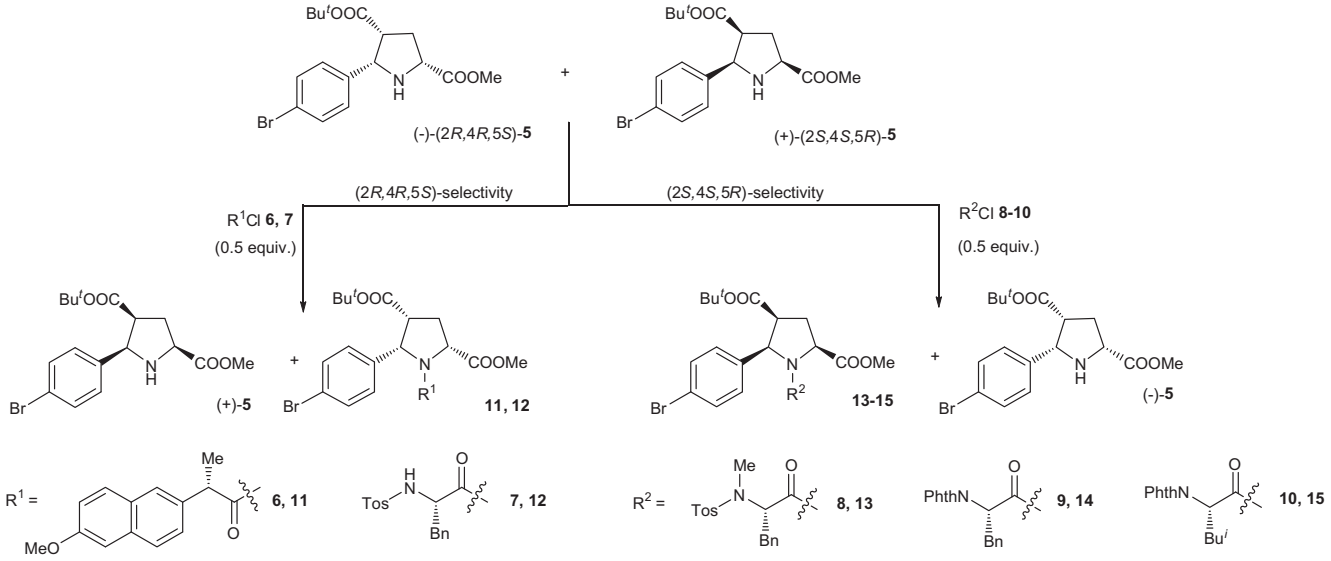
Herein we have studied approaches to individual enantiomers of all-*cis*-pyrrolidine **5**[7] (Scheme 1), which is a key precursor in the synthesis of small-molecule thrombin inhibitors,[4] based on chiral HPLC and acylative kinetic resolution (KR) of the racemate.

Due to our experience in the acylative KR[8] of racemic heterocyclic amines, such as 2-methyl-1,2,3,4-tetrahydroquinoline, 3-methyl-2*H*-[1,4]benzoxazines and 2-methylindoline under the action of 2-arylpropionyl[9] and N-protected (*S*)-amino acyl chlorides[10] as chiral resolving agents (CRAs), we decided to use this methodology to prepare the enantiomers of pyrrolidine **5**. It was especially of interest, because our earlier attempts for acylative KR of racemic secondary amines without a condensed aromatic system, such as 2-methylpiperidine, were unsuccessful.[9d]

2. Results and discussion

For the acylative KR of racemic pyrrolidine **5** we used (*S*)-naproxen acyl chloride **6** and acyl chlorides **7**–**10** of N-protected (*S*)-amino acids (*N*-tosyl-(*S*)-phenylalanine, *N*-methyl-*N*-tosyl-(*S*)-phenylalanine, *N*-phthaloyl-(*S*)-phenylalanine and *N*-phthaloyl-(*S*)-leucine) as CRAs. The preparation of acyl chlorides **6**,[9a] **9**[10c] and **10**[10e] has already been described. Acyl chlorides **7** and **8** were prepared in good yields by the reaction of the appropriate N-protected amino acids with oxalyl chloride in benzene in the presence of catalytic amounts of DMF followed by recrystallization from a hexane–CH_2Cl_2 mixture.

Acylation of racemic pyrrolidone **5** using acyl chlorides **6**–**10** at an amine–acyl chloride molar ratio of 2:1 was carried out in toluene or dichloromethane at +20 °C for 6 h (Scheme 1). The initial concentration of racemic pyrrolidone **5** was 0.1 M. After treatment of the reaction mixtures, we determined the diastereoisomeric excess (*de*, %) of amides **11**–**15** (HPLC) and the enantiomeric excess (*ee*, %) of the unreacted amine **5** (chiral HPLC) (see Table 1). Based on these data, the conversion of racemic substrate **5** (*C*, %) and the



Scheme 1. Acylative kinetic resolution of all-*cis*-4-*tert*-butoxycarbonyl-2-methoxycarbonyl-5-(4-bromophenyl)pyrrolidine **5** with chiral acyl chlorides **6**–**10**.

Table 1
Results of the kinetic resolution of racemic amine **5** via acylation with acyl chlorides **6**–**10** at +20 °C[a]

Entry	Chiral resolving agent	Solvent	Amide, *de* %[b] (configuration)	Unreacted **5**, *ee* %[c] (configuration)	Conversion, *C* %	Selectivity factor, *s*
1	**6**	Toluene	43.0 (2′*S*,2*R*,4*R*,5*S*)	20.8 (2*S*,4*S*,5*R*)	32	3.1
2	**6**	CH_2Cl_2	0	0	nd	—
3	**7**	Toluene	9.5 (2′*S*,2*R*,4*R*,5*S*)	8.7 (2*S*,4*S*,5*R*)	48	1.3
4	**7**	CH_2Cl_2	18.6 (2′*S*,2*R*,4*R*,5*S*)	18.0 (2*S*,4*S*,5*R*)	49	1.7
5	**8**	Toluene	53.5 (2′*S*,2*S*,4*S*,5*R*)	42.6 (2*R*,4*R*,5*S*)	44	5.0
6	**8**	Toluene[d]	42.0 (2′*S*,2*S*,4*S*,5*R*)	88.2 (2*R*,4*R*,5*S*)	68	6.5
7	**8**	CH_2Cl_2	12.4 (2v*S*,2*S*,4*S*,5*R*)	7.2 (2*R*,4*R*,5*S*)	37	1.4
8	**9**	Toluene	55.0 (2′*S*,2*S*,4*S*,5*R*)	37.5 (2*R*,4*R*,5*S*)	41	4.8
9	**9**	Toluene[d]	55.4 (2′*S*,2*S*,4*S*,5*R*)	81.0 (2*R*,4*R*,5*S*)	59	8.3
10	**9**	CH_2Cl_2	38.2 (2′*S*,2*S*,4*S*,5*R*)	20.8 (2*R*,4*R*,5*S*)	35	2.7
11	**10**	Toluene	52.0 (2′*S*,2*S*,4*S*,5*R*)	19.6 (2*R*,4*R*,5*S*)	27	3.9
12	**10**	CH_2Cl_2	33.8 (2′*S*,2*S*,4*S*,5*R*)	17.8 (2*R*,4*R*,5*S*)	34	2.4

[a] Average values for 2–4 parallel runs are presented.
[b] Determined by HPLC (Reprosil 100Si, see Section 4).
[c] Determined by chiral HPLC (Chiralcel OD-H, see Section 4).
[d] Amine **5**–acyl chloride–*N*,*N*-diethylaniline molar ratio of 1:0.75:0.75, −20 °C, 48 h.

selectivity factor (s) were calculated according to Kagan's equations:

$$C = [ee_{amine}/(ee_{amine} + de_{amide})] \times 100\%;$$

$$s = \ln[(1 - C) \times (1 - ee_{amine})]/\ln[(1 - C) \times (1 + ee_{amine})].$$[11]

It has been found that acyl chlorides **6** and **7** preferentially reacted with (2*R*,4*R*,5*S*)-**5**, whereas acyl chlorides **8**–**10** reacted with the (2*S*,4*S*,5*R*)-isomer (according to the chiral HPLC of unreacted pyrrolidone **5**). In the acylation of racemic pyrrolidone **5** with (*S*)-naproxen acyl chloride **6**, the selectivity factor and conversion of the racemic substrate significantly depended on the solvent nature. Thus, acylation occurred with moderate selectivity (s 3.1) in toluene (amide **11**, 43.0% *de*), and the enantiomeric excess of remaining (2*S*,4*S*,5*R*)-**5** was 20.8% (Table 1, entry 1). However, the acylation of racemic pyrrolidine **5** with acyl chloride **6** was unselective in CH_2Cl_2. Acylation with *N*-tosyl-(*S*)-phenylalanyl chloride **7** was inefficient both in toluene and dichloromethane, s 1.3–1.7, *de* of amide **13** was less 18.6% (Table 1, entries 3 and 4).

In the case of *N*-methyl-*N*-tosyl-(*S*)-phenylalanyl **8** and *N*-phthaloyl-(*S*)-phenylalanyl **9** chlorides, the acylation took place most selectively in toluene: the *de* of amides **14** and **15** was 53.5% and 55.0%, respectively, (s 5.0 and 4.8); *ee* of unreacted amine **5** was 42.6% and 37.5%, respectively (Table 1, entries 5 and 8). The KR with *N*-phthaloyl-(*S*)-leucyl chloride **10** (Table 1, entries 11 and 12) proceeded with lower selectivity (s less 3.9) and conversion as compared to *N*-phthaloyl-(*S*)-phenylalanyl chloride **9**.

In order to obtain individual diastereoisomeric amides, we carried out the acylation of racemic pyrrolidine **5** with equimolar amounts of acyl chlorides **6**–**10** in the presence of *N*,*N*-diethylaniline as an acceptor of HCl. Both diastereoisomers of amides **11**, **14** and **15** were isolated from their mixtures by column flash-chromatography on silica gel (benzene–EtOAc as an eluent) or recrystallization. However, we failed to separate the diastereoisomeric mixtures of amides **12** and **13** either by recrystallization or by chromatography.

Since the results of the KR of racemic pyrrolidine **5** with acyl chlorides **6**–**10** as CRAs were not encouraging, we decided to isolate the enantioenriched unreacted amine **5** after acylation of the racemate with 0.75 equiv of acyl chloride **8** or **9** in the presence of 0.75 equiv of *N*,*N*-diethylaniline in toluene at +20 °C. As a result, the *ee* of unreacted amine **5** was 88.2 and 81.0% in the cases of acyl chlorides **8** and **9**, respectively (Table 1, entries 6 and 9). However, the preparative chromatographic isolation of unreacted amine **5** from the reaction mixture was laborious, and the yield of enantioenriched pyrrolidine **5** was no more than 13% relative to the starting racemate. Nevertheless, we have shown the fundamental possibility of the KR of a heterocyclic non-aromatic amine in the diastereoselective acylation with chiral acyl chlorides.

Since the KR approach proved inefficient from a practical point of view, we carried out a preparative HPLC separation of the enantiomers of pyrrolidine **5** on a Chiralcel OD-H column (20 × 250 mm, 5 μm) using hexane–isopropanol 10:1 as an eluting solvent. The enantiomers of all-*cis*-pyrrolidine **5** were obtained from 300 mg of racemate: 114 mg of (+)-(2*S*,4*S*,5*R*)-**5**, *ee* >99.8% (t_R = 31 min) and 129 mg of (−)-(2*R*,4*R*,5*S*)-**5**, 99.2% *ee* (t_R = 47 min). Previously, (+)-**5** and (−)-**5** enantiomers were synthesized by the asymmetric 1,3-dipolar cycloaddition with 66[12a] and 95% *ee*,[12b] respectively. The assignment of the configuration was made by comparing the specific rotation of the enantiomers with the published data.[12] In addition, the absolute configuration of the stereogenic centres in (+)-(2*S*,4*S*,5*R*)-**5** was established by X-ray crystallography in experiments with anomalous scattering

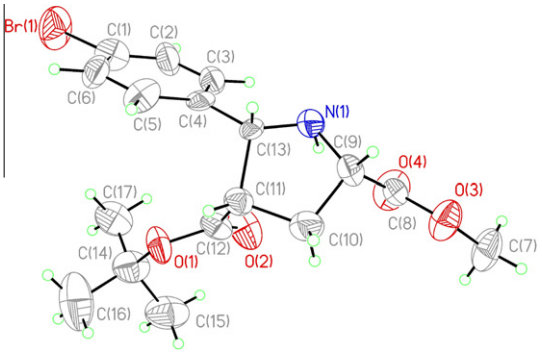


Figure 2. X-ray structure of (+)-(2*S*,4*S*,5*R*)-**5**.

(Fig. 2). The X-ray structure of (−)-(2*R*,4*R*,5*S*)-**5** has already been published.[12b]

3. Conclusion

We have carried out a preparative HPLC resolution to obtain enantiomerically pure (*ee* >99%) enantiomers of all-*cis*-5-(4-bromo-phenyl)-4-*tert*-butoxycarbonyl-2-methoxycarbonylpyrrolidine, a key precursor in the synthesis of small-molecule thrombin inhibitors. We have demonstrated the fundamental possibility of the kinetic resolution of racemic heterocyclic amines without a condensed aromatic system using chiral acyl chlorides as acylating agents.

4. Experimental

4.1. General

All-*cis*-5-(4-bromophenyl)-4-*tert*-butoxycarbonyl-2-methoxycarbonylpyrrolidine **5**,[7] (*S*)-2-(6-methoxynaphth-2-yl)propionyl chloride **6**,[9a] *N*-phthaloyl-(*S*)-phenylalanyl chloride **9**,[10c] *N*-phthaloyl-(*S*)-leucyl chloride **10**,[10e] *N*-tosyl-(*S*)-phenylalanine[13] and *N*-methyl-*N*-tosyl-(*S*)-phenylalanine[13] were synthesized according to the literature. Other reagents are commercially available. The solvents were dried according to standard methods[14] and used as freshly prepared. Flash column chromatography was performed using Silica gel 60 (230–400 mesh) (Alfa Aesar, UK). Melting points were obtained on a SMP3 apparatus (Barloworld Scientific, UK) and are uncorrected. Optical rotations were measured on a Perkin Elmer M341 polarimeter. The ^{1}H NMR spectra were recorded on a Bruker DRX-400 (400 MHz) or Bruker Avance 500 (500 MHz) spectrometer with TMS as an internal reference. The ^{1}H NMR spectra of amides (2′*S*,2*S*,4*S*,5*R*)-**14** and (2′*S*,2*S*,4*S*,5*R*)-**15** were recorded in DMSO-d_6 at 120 °C; the ^{1}H NMR spectra of all of the other compounds were recorded at ambient temperature. Elemental analysis was performed using a Perkin Elmer 2400 II or EuroVector EA3000 analyser. Analytical HPLC of amine **5** and amide **11** was performed on a Knauer Smartline-1100 instrument using a Chiralcel OD-H column (250 × 4.6 mm, 5 μm), detection at 230 nm, 1 mL/min flow rate, *n*-hexane–*i*-PrOH–MeOH 10:0.8:0.2 mixture as eluting solvent. Analytical HPLC of amides **12**–**15** was performed on an Agilent-1100 instrument using a Phenomenex Luna C18 column (250 × 4.6 mm, 5 μm), detection at 230 nm, 0.8 mL/min flow rate, MeCN–H_2O 75:25 mixture 10:0.8:0.2 as eluting solvent.

Preparative HPLC of pyrrolidine **5** was performed at ambient temperature using a chromatograph system consisting of Chiralcel OD-H column (20 × 250 mm, 5 μm) (Daicel Corporation, Japan), Gilson-305 pump (France), injector with the 2.0 mL loop, L-4000A UV Detector (Hitachi, Japan), detection at 230 nm,

6.0 mL/min flow rate, *n*-hexane–*i*PrOH 10:1 mixture as eluting solvent. Retention times for (2*S*,4*S*,5*R*)-**5** and (2*R*,4*R*,5*S*)-**5** were 31 and 47 min, respectively.

Crystallographic data for (2*S*,4*S*,5*R*)-**5** have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 905540). 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].

4.2. (2*S*,4*S*,5*R*)-5-(4-Bromophenyl)-4-*tert*-butoxycarbonyl-2-methoxycarbonylpyrrolidine (2*S*,4*S*,5*R*)-5

Colourless powder (114 mg, 38%): mp 85 °C. 99.8% *ee* (HPLC, Chiralcel OD-H, t_R 8.0 min). $[\alpha]_D^{20} = +31.0$ (*c* 1.0, C_6H_6); +30.3 (*c* 0.75, CH_2Cl_2) {lit.[12a] $[\alpha]_D = +18$ (*c* 0.76, CH_2Cl_2), 66% *ee*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.00 (s, 9H, COO^{t}Bu); 2.15 (ddd, 1H, *J* 12.5, 8.4 and 7.9 Hz, H-3B); 2.26 (m, 1H, H-3A); 3.21 (m, 1H, H-4); 3.69 (s, 3H, COOMe); 3.86 (dd, 1H, *J* 8.4 and 8.4 Hz, H-2); 4.43 (d, 1H, *J* 8.5 Hz, H-5); 7.30 (m, 2H, Ar); 7.50 (m, 2H, Ar). Anal. Calcd for $C_{17}H_{22}BrNO_4$ (384, 26): C, 53.14; H, 5.77; N, 3.65. Found: C, 53.42; H, 6.02; N, 3.59.

4.3. (2*R*,4*R*,5*S*)-5-(4-Bromophenyl)-4-*tert*-butoxycarbonyl-2-methoxycarbonylpyrrolidine (2*R*,4*R*,5*S*)-5

Colourless powder (129, 43%): mp 85 °C. 99.2% (HPLC, Chiralcel OD-H, t_R 10.4 min). $[\alpha]_D^{20} = -33.0$ (*c* 1.0, C_6H_6). {lit.[12b] $[\alpha]_D^{20} = -23.2$ (*c* 0.5, CH_2Cl_2), 95% *ee*.}. ^{1}H NMR spectrum was identical to the spectrum of (2*S*,4*S*,5*R*)-**5**.

4.4. Acyl chlorides 7 and 8: general procedure

Oxalyl chloride (0.18 mL, 2.1 mmol) and DMF (3 μl) were added to a suspension of *N*-tosyl-(*S*)-phenylalanine or *N*-methyl-*N*-tosyl-(*S*)-phenylalanine (1 mmol) in benzene (7 mL). The reaction mixture was stirred at ambient temperature for 5–7 h and then evaporated under reduced pressure. The residue was recrystallized from a hexane–CH_2Cl_2 mixture.

4.4.1. *N*-Tosyl-(*S*)-phenylalanyl chloride 7

Pale pink powder (0.306 g, 90.6%): mp 134–135 °C (hexane–CH_2Cl_2) (lit.[15] mp 132.5–133.5 °C). $[\alpha]_D^{20} = +14.9$ (*c* 2.0, C_6H_6). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 s (3H, Tos); 3.17 (2H, d, *J* 6.0 Hz, C^3H_2); 4.52 (1H, dt, *J* 9.7 and 6.0 Hz, C^2H); 4.97 (1H, d, *J* 9.7 Hz, NH); 7.09 (2H, m, Ph); 7.24 (2H, m, Tos); 7.27 (3H, m, Ph); 7.60 (2H, m, Tos). Anal. Calcd for $C_{16}H_{16}ClNO_3S$ (337.82): C, 56.89; H, 4.77; N, 4.15; Cl, 10.49; S, 9.49. Found: C, 56.84; H, 4.68; N, 4.12; Cl, 10.51; S, 9.69.

4.4.2. *N*-Methyl-*N*-tosyl-(*S*)-phenylalanyl chloride 8

Colourless powder (0.257 g, 73%): mp 86–87 °C (hexane–CH_2Cl_2). $[\alpha]_D^{20} = +45.3$ (*c* 1.1, C_6H_6). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (3H, s, Tos); 2.86 (3H, s, NMe), 2.90 (1H, dd, *J* 14.4 and 9.4 Hz, H-3B); 3.43 (1H, dd, *J* 14.4 and 5.8 Hz, H-3A); 5.25 (1H, dd, *J* 9.4 and 5.8 Hz, H-2); 7.18 (4H, m, 2H-Tos and 2H-Ph); 7.30 (3H, m, Ph); 7.42 (2H, m, Tos). Anal. Calcd for $C_{17}H_{18}ClNO_3S$ (351.85): C, 58.03; H, 5.16; N, 3.98; Cl, 10.08; S, 9.11. Found: C, 57.91; H, 5.09; N, 3.91; Cl, 10.15; S, 9.14.

4.5. Diastereoisomeric amides 11–15: general procedure

A solution of the appropriate acyl chloride (0.8 mmol) in CH_2Cl_2 (3 mL) and a solution of *N*,*N*-diethylaniline (119.4 mg, 0.8 mmol) in CH_2Cl_2 (2 mL) were added to a solution of pyrrolidine **5** (307.4 mg, 0.8 mmol) in CH_2Cl_2 (3 mL) at +20 °C. The reaction mixture was then stirred at +20 °C for 6 h, and then successively washed with 5% $NaHCO_3$ (2 × 3 mL) and water (2 × 3 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Diastereoisomers of amide **11** and inseparable diastereoisomeric mixtures of amides **12** and **13** were obtained after flash-column chromatography on silica gel (benzene–EtOAc as eluent). Amides (2′*S*,2*R*,4*R*,5*S*)-**14** and (2′*S*,2*R*,4*R*,5*S*)-**15** were isolated after crystallization of the reaction products from EtOH; amides (2′*S*,2*S*,4*S*,5*R*)-**14** and (2′*S*,2*S*,4*S*,5*R*)-**15** were isolated from the mother liquor after evaporation of the residue and recrystallization from hexane–EtOAc.

4.5.1. (2*R*,4*R*,5*S*)-5-(4-Bromophenyl)-4-*tert*-butoxy-carbonyl-1-[(2′*S*)-2′-(6″-methoxynaphth-2″-yl)propionyl]-2-methoxy-carbonylpyrrolidine [(2′*S*,2*R*,4*R*,5*S*)-11]

Colourless powder (fast eluting isomer, 0.140 g, 31%): mp 202 °C. $[\alpha]_D^{20} = -132$ (*c* 1.0, C_6H_6). *De* >99.9% (HPLC, Chiralcel OD-H, t_R 17.2 min). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.02 (d, 3H, *J* 6.9 Hz, Me-naproxen); 1.09 (s, 9H, COO*t*Bu); 2.15 (1H, m, H-3A); 2.27 (1H, m, H-3B); 3.44 (1H, ddd, *J* 12.6, 8.9 and 6.5 Hz, H-4); 3.50 (1H, q, *J* 6.9 Hz, CH-naproxen); 3.76 (3H, s, COOMe); 3.87 (3H, s, OMe); 4.32 (1H, dd, *J* 11.1 and 6.8 Hz, H-2); 5.10 (1H, d, *J* 8.9 Hz, H-5); 7.17 (1H, dd, *J* 8.9 and 2.5 Hz, H-3″); 7.31 (1H, d, *J* 2.5 Hz, H-1″); 7.38 (1H, dd, *J* 8.6 and 1.6 Hz, H-7″); 7.67 (5H, m, H-5″ and C_6H_4); 7.80 (1H, d, *J* 8.6 Hz, H-8″); 7.83 (1H, d, *J* 8.9 Hz, H-4″). Anal. Calcd for $C_{31}H_{34}BrNO_6$ (596.51): C, 62.42; H, 5.75; N, 2.35. Found: C, 62.59; H, 5.81; N, 2.35.

4.5.2. (2*S*,4*S*,5*R*)-5-(4-Bromophenyl)-4-*tert*-butoxy-carbonyl-1-[(2′*S*)-2′-(6″-methoxynaphth-2″-yl)propionyl]-2-methoxy-carbonyl-pyrrolidine (2′*S*,2*S*,4*S*,5*R*)-11

Colourless powder (slow eluting isomer, 0.185 g, 41%): mp 170 °C. $[\alpha]_D^{20} = +35.4$ (*c* 1.0, C_6H_6). *De* >99.9% (HPLC, Chiralcel OD-H, t_R 13.3 min). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.13 (9H, s, COO*t*-Bu); 1.33 (3H, d, *J* 6.8 Hz, Me-naproxen); 2.07 (1H, m, H-3B); 2.29 (1H, m, H-3A); 3.63 (1H, ddd, *J* 13.0, 8.8 and 6.4 Hz, H-4); 3.67 (3H, s, COOMe); 3.83 (3H, s, OMe); 3.87 (1H, q, *J* 6.8 Hz, CH-naproxen); 4.35 (1H, dd, *J* 11.5 and 6.7 Hz, H-2); 5.59 (1H, d, *J* 8.8 Hz, H-5); 6.69 (1H, m, H-5″); 6.85 (1H, dd, *J* 8.6 and 1.6 Hz, H-7″); 7.06 (1H, dd, *J* 8.9 and 2.5 Hz, H-3″); 7.14 (1H, d, *J* 2.5 Hz, H-1″); 7.18 (2H, m, C_6H_4); 7.35 (2H, m, C_6H_4); 7.38 (1H, d, *J* 8.9 Hz, H-4″); 7.43 (1H, d, *J* 8.6 Hz, H-8″). Anal. Calcd for $C_{31}H_{34}BrNO_6$ (596.51): C, 62.42; H, 5.75; N, 2.35.Found: C, 62.47; H, 5.77; N, 2.33.

4.5.3. (2*S**,4*S**,5*R**)-5-(4-Bromophenyl)-4-*tert*-butoxy-carbonyl-1-[(2′*S*)-*N*-tosylphenylalanyl]-2-methoxycarbonyl-pyrrolidine 12 (diastereoisomeric mixture)

Colourless powder (0.329 g, 60%): mp 93–102 °C. *Dr* 52:48 [HPLC, Phenomenex Luna C18, t_R 14.5 min (major (2′*S*,2*R*,4*R*,5*S*)-**12**), t_R 16.4 min (minor (2′*S*,2*S*,4*S*,5*R*)-**12**)]. ^{1}H NMR (400 MHz, DMSO-d_6, 120 °C): δ 1.11 (4.7H, s, COO*t*Bu (2′*S*,2*R*,4*R*,5*S*)); 1.14 (4.3H, s, COO*t*Bu (2′*S*,2*S*,4*S*,5*R*)); 2.10–2.42 (6H, m, 2×H-3, H-3′B and Me-Tos); 2.65–2.80 (1H, m, H-3′A, overlapped by water signal); 2.90 (0.52H, m, H-4 (2′*S*,2*R*,4*R*,5*S*)); 3.30 (0.48H, m, H-4(2′*S*,2*R*,4*R*,5*S*)); 3.7 (3H, br s, COOMe); 3.82 (0.48H, m, H-2 (2′*S*,2*S*,4*S*,5*R*)); 3.88 (0.52H, m, H-2 (2′*S*,2*R*,4*R*,5*S*)); 4.15 (0.48H, dd, *J* 10.8 and 7.1 Hz, H-2′ (2′*S*,2*S*,4*S*,5*R*)); 4.30–5.05 (1.04H, m, H-2′ (2′*S*,2*R*,4*R*,5*S*) and H-5 (2′*S*,2*R*,4*R*,5*S*)); 5.24 (0.48H, d, *J* 8.7, H-5 (2′*S*,2*S*,4*S*,5*R*)); 6.30-7.75 (14H, m, Ph, C_6H_4-Tos, C_6H_6-Br and NH). Anal. Calcd for $C_{33}H_{37}BrN_2O_7S$ (685.63): C, 57.81; H, 5.44; N, 4.09; S, 4.68. Found: C, 57.86; H, 5.47; N, 4.13; S, 4.71.

4.5.4. (2*S**,4*S**,5*R**)-5-(4-Bromophenyl)-4-*tert*-butoxy-carbonyl-1-[(2′*S*)-*N*-methyl-*N*-tosylphenylalanyl]-2-methoxy-carbonyl pyrrolidine 13 (diastereoisomeric mixture)

Colourless powder (0.324 g, 58%): mp 91–105 °C. *Dr* 55:45 [HPLC, Phenomenex Luna C18, t_R 22.0 min (major (2′*S*,2*R*,4*R*,5*S*)-**13**), t_R 29.2 min (minor (2′*S*,2*S*,4*S*,5*R*)-**13**)]. ^{1}H NMR (400 MHz,

DMSO-d_6, 120 °C): δ 1.11 (4.0H, s, COO*t*Bu (2′*S*,2*R*,4*R*,5*S*)); 1.14 (5.0H, s, COO*t*Bu (2′*S*,2*S*,4*S*,5*R*)); 2.15–2.40 (5H, m, 2 × H-3 and Me-Tos); 2.47 (0.55H, m, H-3′B (2′*S*,2*S*,4*S*,5*R*), overlapped by DMSO signal); 2.55–2.75 (m, 1H, H-3′A (2′*S*,2*S*,4*S*,5*R*) and H-3′B (2′*S*,2*R*,4*R*,5*S*)); 2.85 (1.35H, s, NMe (2′*S*,2*R*,4*R*,5*S*)); 2.88 (1.65H, s, NMe (2′*S*,2*S*,4*S*,5*R*)); 3.10 (0.9H, m, H-3′A (2′*S*,2*R*,4*R*,5*S*) and H-4 (2′*S*,2*R*,4*R*,5*S*)); 3.50 (0.55H, m, H-4 (2′*S*,2*S*,4*S*,5*R*)); 3.71 (3H, s, COOMe); 4.33 (0.55H, dd, *J* 10.8 and 7.0 Hz, H-2′ (2′*S*,2*S*,4*S*,5*R*)); 4.48 (0.55H, m, H-2 (2′*S*,2*S*,4*S*,5*R*)); 4.67 (0.45H, m, H-2 (2′*S*,2*R*,4*R*,5*S*)); 4.70–5.40 (0.9H, m, H-2′ (2′*S*,2*R*,4*R*,5*S*) and H-5 (2′*S*,2*R*,4*R*,5*S*)); 6.35–7.48 (13H, m, Ph, C_6H_4-Tos, C_6H_6–Br). Anal. calcd for $C_{34}H_{39}BrN_2O_7S$ (699.55): C, 58.37; H, 5.62; N, 4.00; S, 4.58. Found: C, 58.62; H, 5.80; N, 4.01; S, 4.48.

4.5.5. (2*R*,4*R*,5*S*)-5-(4-Bromophenyl)-4-*tert*-butoxy-carbonyl-1-[(2′*S*)-*N*-phthaloylphenylalanyl]-2-methoxycarbonyl-pyrrolidine (2′*S*,2*R*,4*R*,5*S*)-14

Colourless powder (0.185 g, 35%): mp 287 °C (decomp.) (EtOH). $[\alpha]_D^{20} = -223$ (*c* 1.0, C_6H_6). *De* >99.9% (HPLC, Phenomenex Luna C18, t_R 15.0 min). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (9H, s, COO*t*Bu); 1.84 (1H, m, H-3B); 2.25 (1H, m, H-3A); 3.06 (1H, dd, *J* 13.9 and 11.2 Hz, H-3′B); 3.23 (1H, dd, *J* 13.9 and 4.4 Hz, H-3′A); 3.47 (1H, m, H-4); 3.76 (3H, s, COOMe); 4.35 (1H, dd, *J* 11.8 and 6.7 Hz, H-2); 5.06 (1H, d, *J* 7.8 Hz, H-5); 5.38 (1H, dd, *J* 10.7 and 4.4 Hz, H-2′); 6.88 (2H, m, Ph); 6.98 (2H, m, C_6H_4); 7.07 (3H, m, Ph); 7.15 (2H, m, C_6H_4); 7.42 (2H, m, Phth); 7.63 (2H, m, Phth). Anal. Calcd for $C_{34}H_{33}BrN_2O_7$ (661.54): C, 61.73; H, 5.03; N, 4.23. Found: C, 61.54; H, 4.82; N, 4.08.

4.5.6. (2*S*,4*S*,5*R*)-5-(4-Bromophenyl)-4-*tert*-butoxy-carbonyl-1-[(2′*S*)-*N*-phthaloylphenylalanyl]-2-methoxycarbonyl-pyrrolidine (2′*S*,2*S*,4*S*,5*R*)-14

Colourless powder (0.213 g, 40%): mp 186–188 °C (hexane–EtOAc). $[\alpha]_D^{20} = +52.4$ (*c* 1.0, C_6H_6). 94.5% *de* (HPLC, Phenomenex Luna C18, t_R 21.0 min). ^{1}H NMR (400 MHz, DMSO-d_6, 120 °C): δ 1.12 (9H, s, COO*t*Bu); 2.29 (1H, m, H-3B); 2.40 (1H, m, H-3A); 2.8 (1H, m, H-3′B, overlapped by water signal); 3.48 (1H, dd, *J* 14.3 and 10.0 Hz, H-3′A); 3.47 (1H, m, H-4); 3.65 (3H, s, COOMe); 4.45 (1H, dd, *J* 9.5 and 7.7 Hz, H-2); 4.97 (1H, dd, *J* 10.1 and 5.0 Hz, H-2′); 5.52 (1H, d, *J* 8.9 Hz, H-5); 6.70 (2H, m, Ph); 7.04 (3H, m, Ph); 7.52 (4H, m, C_6H_4); 7.79 (4H, m, Phth). Anal. Calcd for $C_{34}H_{33}BrN_2O_7$ (661.54): C, 61.73; H, 5.03; N, 4.23. Found: C, 61.79; H, 4.89; N, 4.03.

4.5.7. (2*R*,4*R*,5*S*)-5-(4-Bromophenyl)-4-*tert*-butoxy-carbonyl-1-[(2′*S*)-*N*-phthaloylleucyl]-2-methoxycarbonyl-pyrrolidine (2′*S*,2*R*,4*R*,5*S*)-15

Colourless powder (0.201 g, 40%): mp 242 °C (decomp.) (EtOH). $[\alpha]_D^{20} = -54.5$ (*c* 0.5, C_6H_6). *De* >99.9% (HPLC, Phenomenex Luna C18, t_R 15.2 min). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.80 (3H, d, *J* 6.6 Hz, Me-4′); 0.87 (3H, d, *J* 6.4 Hz, Me-4′); 1.17 (9H, s, COO*t*Bu); 1.23 (1H, m, H-3′B); 1.75 (2H, m, H-3′A and H-4′); 1.84 (1H, m, H-3B); 2.22 (1H, m, H-3A); 3.51 (1H, m, H-4); 3.74 (3H, s, COOMe); 4.29 (1H, dd, *J* 12.1 and 6.7 Hz, H-2); 5.10 (2H, m, H-2′ and H-5); 6.94 (2H, m, C_6H_4); 7.20 (2H, m, C_6H_4); 7.53 (2H, m, Phth); 7.70 (2H, m, Phth). Anal. Calcd for $C_{31}H_{35}BrN_2O_7$ (627.52): C, 59.33; H, 5.62; N, 4.46. Found: C, 59.31; H, 5.57; N, 4.43.

4.5.8. (2*S*,4*S*,5*R*)-5-(4-Bromophenyl)-4-*tert*-butoxy-carbonyl-1-[(2′*S*)-*N*-phthaloylleucyl]-2-methoxycarbonyl-pyrrolidine (2′*S*,2*S*,4*S*,5*R*)-15

Colourless powder (0.215 g, 43%): mp 187–188 °C (hexane–EtOAc). $[\alpha]_D^{20} = +58.5$ (*c* 1.0, C_6H_6). 97.1% *de* (HPLC, Phenomenex Luna C18, t_R 20.8 min). ^{1}H NMR (400 MHz, DMSO-d_6, 120 °C): δ 0.42 (3H, d, *J* 5.9 Hz, Me-4′); 0.58 (3H, d, *J* 6.2 Hz, Me-4′); 1.15 (9H, s, COO*t*Bu); 1.17–1.32 (2H, m, H-3′B and H-4′); 2.19–2.42 (2H, m, H-3′B and 2 × H-3); 3.56 (1H, ddd, *J* 11.7, 8.9 and 6.8 Hz, H-4); 3.69 (3H, s, COOMe); 4.41 (1H, dd, *J* 10.1 and 7.2 Hz, H-2); 4.72 (1H, dd, *J* 10.3 and 4.4 Hz, H-2′); 5.50 (1H, d, *J* 8.9 Hz, H-5); 7.56 (4H, m, C_6H_4); 7.83 (4H, m, Phth). Anal. Calcd for $C_{31}H_{35}BrN_2O_7$ (627.52): C, 59.33; H, 5.62; N, 4.46. Found: C, 59.54; H, 5.64; N, 4.47.

4.6. Kinetic resolution of racemic amine 5: general procedure

A solution of the appropriate acyl chloride (0.05 mmol) in the chosen solvent (0.5 mL) was added to a solution of amine **5** (38.4 mg, 0.1 mmol) in the same solvent (0.5 mL) at +20 °C. The reaction mixture was kept at +20 °C for 6 h, and then washed with 5% $NaHCO_3$ (2 × 3 mL) and water (2 × 3 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give a mixture of diastereoisomeric amides **11**–**15** and unreacted amine **5**, which were analysed by HPLC. Each experiment was performed in 2–4 runs.

4.7. Enantioenriched pyrrolidine (2*R*,4*R*,5*S*)-5: general procedure

A solution of acyl chloride **8** (127.7 mg, 0.363 mmol) in toluene (2 mL) and a solution of $PhNEt_2$ (54.2 mg, 0.363 mmol) in toluene (0.8 mL) were added to a solution of amine **5** (186.1 mg, 0.484 mmol) in toluene (2 mL) at −20 °C. The reaction mixture was then kept at −20 °C for 48 h, and then washed with 5% $NaHCO_3$ (2 × 3 mL) and water (2 × 3 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Flash-column chromatography (benzene–EtOAc as eluent) of the acylation product gave 24.9 mg (13.4%) of unreacted amine (2*R*,4*R*,5*S*)-**5** of 88.2% *ee*.

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