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Substituent effect on the stereoselectivity of acylation of racemic heterocyclic amines with *N*-phthaloyl-3-aryl-(*S*)-alanyl chlorides

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ABSTRACT

The acylative kinetic resolution of racemic 2-methyl-1,2,3,4-tetrahydroquinoline and 2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine using acyl chlorides of *N*-phthaloyl-(*S*)-phenylalanine, *N*-phthaloyl-3-(4-nitrophenyl)-(*S*)-alanine and *N*-phthaloyl-*O*-methyl-(*S*)-tyrosine as chiral resolving agents has been carried out. It is shown that the effectiveness of an acylative kinetic resolution depends on the electronic effects of substituents in the phenyl fragment of the acylating agent and increases as the electron-donating properties of the *para*-substituent (OMe > H > NO_2) in phenyl fragment of *N*-phthaloyl-3-aryl-(*S*)-alanyl chlorides increase; conducting the process at a reduced temperature also contributes to an enhancement of the kinetic resolution.

1. Introduction

Kinetic resolution has been widely used for preparation of enantio pure compounds from the racemates.[1] In particular, acylative kinetic resolution using enzymes,[2] chiral acyl transfer catalysts[3] and chiral acylating agents[4] is frequently applied for obtaining enantiomerically pure amines and their derivatives.

We have shown that chiral acyl chlorides are efficient and convenient acylating resolving agents for the kinetic resolution of a number of racemic heterocyclic amines, such as 2-methyl-1,2,3,4-tetrahydroquinoline **1** and 2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine **2**. It should be noted that enantiopure 2-substituted 1,2,3,4-tetrahydroquinolines[5] and 3-substituted 2,3-dihydro-1,4-benzoxazines[6] are of special interest as the structural fragments of naturally occurring substances and biologically active compounds. It has been found that it is possible to achieve efficient kinetic resolution with the acyl chlorides of (*S*)-naproxen,[7] *N*-tosyl-(*S*)-proline,[8] *N*-phthaloyl-(*S*)-alanine[9] and *N*-phthaloyl-(*S*)-phenylalanine **3**.[10] Previously we have shown that the stereochemical outcome of the kinetic resolution is determined by the structure of the resolving agent. Thus, when the acyl chlorides of (*S*)-naproxen, *N*-phthaloyl-(*S*)-alanine and *N*-phthaloyl-(*S*)-phenylalanine were used as resolving agents, the (*S*)-enantiomers of racemic amines **1** and **2** reacted faster than the (*R*)-amines. In the case of *N*-tosyl-(*S*)-prolyl chloride, (*R*)-**1** and **2** formed products faster than the (*S*)-enantiomers. By this means it provides a possibility for preparative synthesis of both enantiomers of amines **1** and **2**. However, the study of not only structural but also electronic factors is likely to be required for more fundamental understanding of kinetic resolution processes.

Herein we present the results of our studies on the effects of substituents in the phenyl fragment of *N*-phthaloyl-3-aryl-(*S*)-alanyl chlorides **3**–**5** on the stereochemical features of the kinetic resolution of racemic amines **1** and **2**. Thereto, in addition to the previously studied acyl chloride **3**[10] we synthesised acyl chlorides of *N*-phthaloyl-3-(4-nitrophenyl)-(*S*)-alanine **4** and *N*-phthaloyl-*O*-methyl-(*S*)-tyrosine **5** differing in the electronic effects of a substituent in the *para*-position of the phenyl ring, which does not have immediate steric effects.

2. Results and discussion

The acylation of heterocyclic amines with acyl chlorides **3**–**5** was carried out in various solvents at either +20 or −20 °C (Scheme 1). In all cases, the formation of the mixtures of diastereoisomeric amides enriched with (*S*,*S*)-diastereoisomers was observed, while unreacted amines were enriched with (*R*)-enantiomers (according to chiral HPLC). Individual (*S*,*S*)-amides **6** and **7** were previously isolated by the recrystallisation of the mixtures of diastereoisomeric amides.[10] However, in the cases of amides **8**–**11** we were unsuccessful in isolating the pure (*S*,*S*)-amides either by recrystallisation or by column chromatography. Therefore, we specially obtained (*S*,*S*)-amides **8**–**11** starting from enantio pure amines (*S*)-**1**[10] and (*S*)-**2**.[9]

Based on the data for the kinetic resolution of amine **1** at +20 °C, it was established that acyl chloride **4** (R = NO_2) is a less selective acylating agent in comparison with unsubstituted acyl chloride

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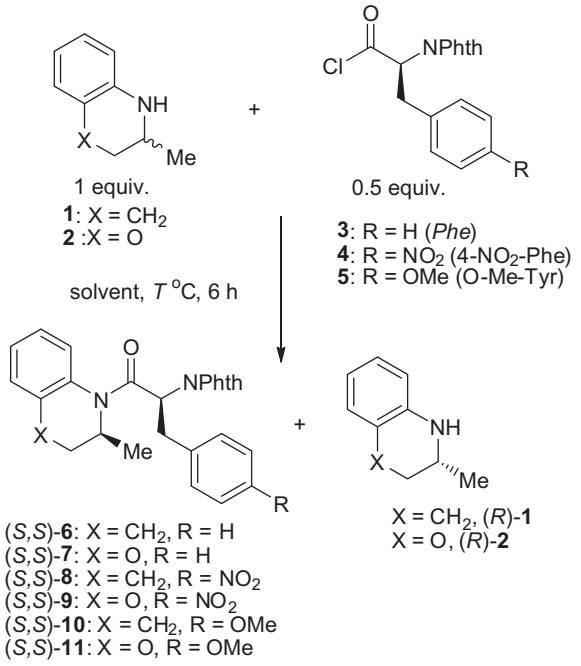

Scheme 1. Acylative kinetic resolution of racemic amines **1** and **2** with chiral acyl chlorides **3**–**5**.

3; however compound **5** (R = OMe) exhibited a somewhat greater stereoselectivity than **3** (Table 1, entries 1–16).

For example, when the acylation was carried out in dichloromethane at +20 °C the selectivity factor *s* was 8.9, 6.9 and 9.7 for acyl chlorides **3**, **4** and **5**, respectively. Acylation of amine **2** proceeded in a similar way (Table 1, entries 17–28). In all cases the best stereochemical results were obtained in either dichloromethane or acetonitrile. A decrease in $de_{(S,S)\text{-amide}}$, *C* and *s* values was observed when the kinetic resolution experiments were carried out in benzene or toluene. It is known that aromatic π–π interactions were strongly manifested in polar solvents, however benzene and toluene molecules are supposed to solvate the aryl groups of the dissolved substances more effectively, thus preventing the π–π interactions.[11,12]

In all cases, lowering the reaction temperature led to an increase in the acylation stereoselectivity (Table 1, entries 11–16 and 23–28). Thus, for example, when the acylation of amine **1** with acyl chloride **5** was carried out in dichloromethane $de_{(S,S)\text{-}\mathbf{10}}$ was 70.7% and 75.5% (*s* 9.7 and 13.7) at +20 and −20 °C, respectively (Table 1, entries 9 and 16). The kinetic resolution of amine **2** with chiral acyl chlorides in dichloromethane at +20 °C also demonstrated stereoselectivity in the order **4** < **3** < **5**, thus providing *s* values 4.2, 6.0 and 6.3, respectively (Table 1, entries 19, 17 and 21).

The decrease in the stereoselectivity of the acylation of heterocyclic amines **1** and **2** with the resolving agent **4** with an electron-withdrawing substituent R = NO_2 as compared with **3** (R = H), and the increase when using methoxy-substituted derivative **5** (R = OMe) can be considered as an argument in favour of specific π–π aromatic interactions contributing to the process of enantiomeric differentiation. It also indicates that both electronic and steric effects are involved in the acylative kinetic resolution. This should be taken into consideration when designing new chiral resolving agents.

3. Conclusion

In conclusion, the acylative kinetic resolution of racemic 2-methyl-1,2,3,4-tetrahydroquinoline and 2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine using acyl chlorides of *N*-phthaloyl-(*S*)-phen-

Table 1
Results for the kinetic resolution of racemic amines **1** and **2** using acyl chlorides **3**–**5**[a]

Entry	Racemic amine	Resolving agent	*T* (°C)	Solvent	(*S*,*S*)-Amide, de[b] (%)	Unreacted (*R*)-amine, ee[c] (%)	Conversion, *C*[d] (%)	Selectivity factor, *s*[e]
1	**1**	**3**	+20	Toluene	48.8	33.3	40	4.1[10]
2	**1**	**3**	+20	CH_2Cl_2	67.1	56.9	46	8.9[10]
3	**1**	**4**	+20	Toluene	42.2	33.1	44	3.3
4	**1**	**4**	+20	Benzene	54.3	36.3	40	4.8
5	**1**	**4**	+20	CH_2Cl_2	62.0	50.4	45	6.9
6	**1**	**4**	+20	MeCN	65.3	60.6	48	8.6
7	**1**	**5**	+20	Toluene	54.0	34.6	39	4.6
8	**1**	**5**	+20	Benzene	64.4	47.9	43	7.2
9	**1**	**5**	+20	CH_2Cl_2	70.7	51.3	42	9.7
10	**1**	**5**	+20	MeCN	68.7	54.2	44	9.2
11	**1**	**3**	−20	Toluene	68.9	33.3	33	7.6[10]
12	**1**	**3**	−20	CH_2Cl_2	74.4	60.4	45	12.5[10]
13	**1**	**4**	−20	Toluene	54.5	37.2	41	4.8
14	**1**	**4**	−20	CH_2Cl_2	69.0	59.2	46	9.9
15	**1**	**5**	−20	Toluene	69.4	32.8	32	7.6
16	**1**	**5**	−20	CH_2Cl_2	75.5	63.6	46	13.7
17	**2**	**3**	+20	CH_2Cl_2	59.2	47.5	45	6.0[10]
18	**2**	**3**	+20	MeCN	59.8	48.7	45	6.3[10]
19	**2**	**4**	+20	CH_2Cl_2	47.8	40.9	46	4.2
20	**2**	**4**	+20	MeCN	52.6	46.1	47	5.0
21	**2**	**5**	+20	CH_2Cl_2	60.5	46.1	43	6.3
22	**2**	**5**	+20	MeCN	60.2	45.6	43	6.2
23	**2**	**3**	−20	CH_2Cl_2	64.3	46.4	42	7.2[10]
24	**2**	**3**	−20	MeCN	67.4	46.2	41	8.1[10]
25	**2**	**4**	−20	CH_2Cl_2	63.0	44.0	41	6.7
26	**2**	**4**	−20	MeCN	62.8	43.1	41	6.6
27	**2**	**5**	−20	CH_2Cl_2	63.8	52.3	45	7.5
28	2	**5**	−20	MeCN	69.4	47.6	41	8.8

[a] Average values for 2–4 parallel runs are presented.
[b] Determined by HPLC (see Section 4).
[c] Determined by chiral HPLC (see Section 4).
[d] $C = ee_{\text{amine unreacted}} \times 100\%/(ee_{\text{amine unreacted}} + de_{\text{amide formed}})$.[1a]
[e] $s = \ln(1 - C) \times (1 - ee_{\text{amine unreacted}})/\ln(1 - C) \times (1 + ee_{\text{amine unreacted}})$.[1a]

ylalanine, *N*-phthaloyl-3-(4-nitrophenyl)-(*S*)-alanine and *N*-phthaloyl-*O*-methyl-(*S*)-tyrosine as chiral resolving agents was carried out. It has been shown that the effectiveness of acylative kinetic resolution depends on the electronic effects of substituents in the phenyl fragment of the acylating agent and increases as the electron-donating properties of the *para*-substituent (OMe > H > -NO_2) in the phenyl fragment of *N*-phthaloyl-3-aryl-(*S*)-alanyl chlorides increase.

4. Experimental

4.1. General

Solvents were dried and purified by standard methods. 3-(4-Nitrophenyl)-(*S*)-alanine[13] and *O*-methyl-(*S*)-tyrosine[14] were obtained according to known procedures. Compounds **3**, **6** and **7** were described previously.[10] Enantiomerically pure amines (*S*)-**1**[10] and (*S*)-**2**[9] were prepared as described previously. All other reagents were of commercial quality. Melting points were obtained using an SMP3 apparatus (Barloworld Scientific, UK) and are uncorrected. Optical rotations were measured at a sodium D line with Perkin Elmer M 341 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-400 or Bruker Avance 500 spectrometers with tetramethylsilane as an internal standard. *J* values are given in Hz. ^{1}H and ^{13}C NMR spectra of amides **8**–**11** were recorded in DMSO-d_6 at 100 °C. All the ^{1}H and ^{13}C signals of compounds (*S*,*S*)-**8**–**11** were assigned on the basis of 2D ^{1}H–^{13}C HSQC and HMBC experiments at 100 °C. ^{1}H NMR spectra of *N*-phthaloyl-(*S*)-amino acids and acyl chlorides **4** and **5** were recorded at ambient temperature. Elemental analyses were performed on a Euro EA 3000 element analyzer (Eurovector, Italy).

Analytical HPLC was performed on a Knauer Smartline-1100 instrument using a ReproSil 100 Si column (250 × 4.6 mm) for amides **8**–**11**, detection at 220 nm, 1 mL/min flow rate, *n*-hexane/*i*-PrOH 80:1 as an eluting solvent; and a Chiralcel OD-H column (250 × 4.6 mm) for amines **1** and **2**, detection at 220 nm, 1 mL/min flow rate, *n*-hexane/*i*-PrOH/MeOH 140:0.7:0.3 ($\tau_{(R)\text{-}\mathbf{1}}$ 9.5–9.6 min, $\tau_{(S)\text{-}\mathbf{1}}$ 10.5–10.7 min) and 100:1.5:1.5 ($\tau_{(R)\text{-}\mathbf{2}}$ 9.6–9.8 min, $\tau_{(S)\text{-}\mathbf{2}}$ 10.5–10.6 min) as eluting solvents.

4.2. *N*-Phthaloyl-(*S*)-amino acids. General procedure

N-Carbethoxyphthalimide (6 mmol) was added to a stirred solution of amino acid (6 mmol) and Na_2CO_3 (6 mmol) in water (50 mL) at room temperature. The reaction mixture was stirred for 2–3 h and then filtered off. The filtrate was acidified with 4 N HCl up to pH 1–2. The precipitate was filtered off, recrystallised from EtOH–H_2O and dried in vacuum at 60 °C.

4.2.1. *N*-Phthaloyl-3-(4-nitrophenyl)-(*S*)-alanine

Colourless crystals (1.35 g, 66%): mp 207–208 °C (EtOH–H_2O) (lit.[15a] mp 204.7 °C;[15b] 209–211 °C). $[\alpha]_D^{20} = -231.0$ (*c* 1.3, EtOH) {lit.,[15b] $[\alpha]_D^{20} = -233 \pm 2$ (EtOH)}. Anal. Calcd for $C_{17}H_{12}N_2O_6$: C, 60.00; H, 3.55; N, 8.23. Found: C, 59.75; H, 3.41; N, 8.26. ^{1}H NMR (400 MHz; DMSO-d_6): δ 3.47 (1H, dd, *J* 14.2 and 11.4, H^B-3), 3.63 (1H, dd, *J* 14.2 and 4.9, H^A-3), 5.24 (1H, dd, *J* 11.4 and 4.9, H-2), 7.49 (2H, m, Ar), 7.86 (4H, m, Phth), 8.07 (2H, m, Ar), 13.49 (1H, br s, COOH).

4.2.2. *O*-Methyl-*N*-phthaloyl-(*S*)-tyrosine

Colourless crystals (1.46 g, 75%): mp 127–128 °C (EtOH–H_2O) (lit.[16] 128 °C). Anal. Calcd for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.65; N, 4.31. Found: C, 66.40; H, 4.48; N, 4.41. $[\alpha]_D^{20} = -214.8$ (*c* 1.0, CH_2Cl_2) {lit.[16] $[\alpha]_D = -210.2$ (*c* 1, CH_2Cl_2)}. ^{1}H NMR (400 MHz; DMSO-d_6): δ 3.28 (1H, dd, *J* 14.2 and 11.8, H^B-3), 3.41 (1H, dd, *J* 14.2 and 4.8, H^A-3), 3.63 (3H, s, OMe), 5.06 (1H, dd, *J* 11.8 and 4.8, H-2), 6.73 (2H, m, Ar), 7.06 (2H, m, Ar), 7.85 (4H, m, Phth), 13.35 (1H, br s, COOH).

4.3. Acyl chlorides. General procedure

Oxalyl chloride (0.175 mL, 2 mmol) was added to a stirred suspension of *N*-phthaloyl-(*S*)-amino acid (1 mmol) in a mixture of benzene/*n*-hexane 6:4 (8 mL) at room temperature and then DMF (2 μL) was added to the reaction mixture. The reaction mixture was stirred for 6 h at room temperature, and then the reaction solution was evaporated to dryness under reduced pressure. The residue was treated with *n*-hexane to give acyl chlorides **4** and **5**. Freshly prepared acyl chlorides were used for further syntheses without additional purification.

4.3.1. 3-(4-Nitrophenyl)-*N*-phthaloyl-(*S*)-alanyl chloride 4

Pale-yellow oil (0.344 g, 96%). ^{1}H NMR (400 MHz; $CDCl_3$): δ 3.69 (1H, dd, *J* 14.4 and 10.6, H^B-3), 3.75 (1H, dd, *J* 14.4 and 5.6, H^A-3), 5.36 (1H, dd, *J* 10.6 and 5.6, H-2), 7.35 (2H, m, Ar), 7.78 (2H, m, Phth), 7.86 (2H, m, Phth), 8.09 (2H, m, Ar).

4.3.2. *O*-Methyl-*N*-phthaloyl-(*S*)-tyrosyl chloride 5

Pale-yellow powder (0.327 g, 95%): mp 82.5–83.5 °C (lit.[17] 81–82 °C). ^{1}H NMR (400 MHz; $CDCl_3$): δ 3.49 (1H, dd, *J* 14.3 and 10.8, H^B-3), 3.59 (1H, dd, *J* 14.3 and 5.3, H^A-3), 3.71 (3H, s, OMe), 5.28 (1H, dd, *J* 10.8 and 5.3, H-2), 6.73 (2H, m, Ar), 7.05 (2H, m, Ar), 7.74 (2H, m, Phth), 7.84 (2H, m, Phth).

4.4. General procedure for studying the kinetic resolution of amines 1 and 2 with acyl chlorides 4 and 5

A solution of acyl chloride **4** or **5** (0.15 mmol) in an appropriate solvent (1.5 mL) was added to a solution of amine **1** or **2** (0.3 mmol) in the same solvent (1.5 mL) at +20 °C or −20 °C. The reaction mixture was kept at a given temperature for 6 h, and then washed consequently with 1 M HCl (3 mL), brine (3 × 3 mL), saturated aqueous $NaHCO_3$ (3 mL) and water (3 × 3 mL). The organic layer was dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give a mixture of diastereoisomeric amides **8**–**11**, the diastereoisomeric ratio of which was analysed by HPLC (ReproSil 100 Si) and ^{1}H NMR. The combined acidic washings were alkalised with Na_2CO_3 and then extracted with $CHCl_3$ (3 × 2 mL). The combined organic extracts were washed with water (2 × 3 mL), dried and evaporated to dryness under reduced pressure to give unreacted amines **1** or **2**, which were analysed by chiral HPLC (Chiralcel OD-H). Each experiment was performed in 2–4 runs.

4.5. Diastereoisomeric amides 8–11. General procedure

The synthesis of mixtures of diastereoisomers **8**–**11** was carried out as described in Section 4.4 starting from amine **1** or **2** (2 mmol) in CH_2Cl_2 (10 mL) and acyl chloride **4** or **5** (1 mmol) in CH_2Cl_2 (10 mL). The reaction was carried out at +20 °C. Amides **8**–**11** were isolated by flash column chromatography on silica gel using a benzene–EtOAc mixture as eluent.

4.5.1. 2-Methyl-1-[3-(4-nitrophenyl)-*N*-phthaloyl-(*S*)-alanyl]-1,2,3,4-tetrahydroquinoline 8 (diastereoisomeric mixture)

Pale-yellow solid (0.315 g, 67%): mp 140–146 °C. Anal. Calcd for $C_{27}H_{23}N_3O_5$: C, 69.07; H, 4.94; N, 8.95. Found: C, 69.15; H, 4.88; N, 8.98. HPLC: $\tau_{(R,S)\text{-}\mathbf{8}}$ 10.3 min and $\tau_{(S,S)\text{-}\mathbf{8}}$ 12.2 min. ^{1}H NMR (500 MHz; DMSO-d_6, 100 °C) [*S*,*S*/*R*,*S* ratio 76:24]: δ 1.00 (0.76H, d, *J* 6.4, Me-*R*,*S*), 1.03 (2.28H, d, *J* 6.6, Me-*S*,*S*), 1.11 (0.24H, m, H^B-3-*R*,*S*), 1.30 (0.76H dddd, *J* 13.1, 10.4, 6.9 and 5.1, H^B-3-*S*,*S*), 2.19 (0.24H, m, H^A-3-*R*,*S*), 2.24–2.36 (1.24H, m, H^A-3-*S*,*S*, H^A-4- and H^B-4-*R*,*S*), 2.48 (overlapped by DMSO, m, H^B-4-*S*,*S*), 2.67 (0.72H,

dt, *J* 15.1 and 5.1, H^A-4-*S*,*S*), 2.81 (0.76H, dd, *J* 14.3 and 4.7, H^B-3′-*S*,*S*). 3.27 (0.24H, dd, *J* 14.1 and 9.4, H^B-3′-*R*,*S*), 3.68 (0.24H, dd, *J* 14.1 and 5.4, H^A-3′-*R*,*S*), 3.85 (0.76H, dd, *J* 14.3 and 11.1, H^A-3′-*S*,*S*), 4.58 (0.24H, m, H-2-*R*,*S*), 4.64 (0.76H, ddq, *J* 7.6, 6.9 and 6.6, H-2-*S*,*S*), 5.60 (0.24H, dd, *J* 9.4 and 5.4, H-2′-*R*,*S*), 5.80 (0.76H, dd, *J* 11.1 and 4.7, H-2′-*S*,*S*), 6.65 (0.24H, d, *J* 7.5, H-5-*R*,*S*), 6.75 (0.24H, td, *J* 7.5 and 1.2, H-6-*R*,*S*), 6.96–7.01 (1.76H, m, H-5′-*S*,*S* and H-7-*R*,*S*), 7.24 (0.24H, d, *J* 7.5, H-8-*R*,*S*), 7.25–7.30 (1.52H, m, H-5- and H-6-*S*,*S*), 7.39 (0.76H, m, H-7-*S*,*S*), 7.43 (0.48H, d, *J* 8.6, H-5′-*R*,*S*), 7.53–7.56 (1.24H, m, H-8-*S*,*S* and H-4″-*R*,*S*), 7.68 (0.48H, m, H-3″-*R*,*S*), 7.83 (3.04H, s, H-3″- and H-4″-*S*,*S*), 7.92 (1.52H, d, *J* 8.8, H-6′-*S*,*S*), 7.97 (0.48H, d, *J* 8.6, H-6′-*R*,*S*).

4.5.2. 2,3-Dihydro-3-methyl-4-[3-(4-nitrophenyl)-*N*-phthaloyl-(*S*)-alanyl]-4*H*-1,4-benzoxazine 9 (diastereoisomeric mixture)

Pale-yellow foam (0.330 g, 70%). Anal. Calcd for $C_{26}H_{21}N_3O_6$: C, 66.24; H, 4.49; N, 8.91. Found: C, 66.33; H, 4.62; N, 8.68. HPLC $\tau_{(R,S)\text{-}\mathbf{9}}$ 9.3 min and $\tau_{(S,S)\text{-}\mathbf{9}}$ 12.8 min. ^{1}H NMR (400 MHz; DMSO-d_6, 100 °C) [*S*,*S*/*R*,*S* ratio 68:32]: δ 0.86 (0.96H, d, *J* 6.7, Me-*R*,*S*), 1.09 (2.04H, d, *J* 6.7, Me-*S*,*S*), 3.36 (0.32H, dd, *J* 14.1 and 9.2, H^B-3′-*R*,*S*), 3.43 (0.68H, dd, *J* 14.2 and 6.1, H^B-3′-*S*,*S*), 3.65 (0.32H, dd, *J* 14.1 and 5.3, H^A-3′-*R*,*S*), 3.85 (0.68H, dd, *J* 14.2 and 9.7, H^A-3′-*S*,*S*), 4.04 (0.68H, dd, *J* 11.0 and 3.3, H^B-2-*S*,*S*), 4.08–4.18 (1.32H, m, H^A-2-*S*,*S*, H^A-2- and H^B-2-*R*,*S*), 4.56 (0.32H, m, H-3-*R*,*S*), 4.75 (0.68H, m, H-3-*S*,*S*), 5.73 (0.32H, dd, *J* 9.2 and 5.3, H-2′-*R*,*S*), 5.81 (0.68H, dd, *J* 9.7 and 6.1, H-2′-*S*,*S*), 6.57 (0.32H, d, *J* 7.9, H-8-*R*,*S*), 6.72 (0.32H, t, *J* 7.8, H-6-*R*,*S*), 6.79–6.86 (1H, m, H-7-*R*,*S* and H-8-*S*,*S*), 6.95 (0.68H, ddd, *J* 8.2, 7.3 and 1.5, H-6-*S*,*S*), 7.10 (0.68H, ddd, *J* 8.2, 7.3 and 1.6, H-7-*S*,*S*), 7.35 (1.36H, d, *J* 8.6, H-5′-*S*,*S*), 7.43 (0.32H, d, *J* 7.9, H-5-*R*,*S*), 7.48 (0.64H, d, *J* 8.6, H-5′-*R*,*S*), 7.67 (0.64H, m, H-4″-*R*,*S*), 7.72–7.77 (1.32H, m, H-5-*S*,*S* and H-3″-*R*,*S*), 7.83 (2.72H, s, H-3″- and H-4″-*S*,*S*), 7.97–8.00 (2H, m H-6′-*S*,*S* and H-6′-*R*,*S*).

4.5.3. 2-Methyl-1-[*O*-methyl-*N*-phthaloyl-(*S*)-tyrosyl]-1,2,3,4-tetrahydroquinoline 10 (diastereoisomeric mixture)

Colourless foam (0.336 g, 74%). Anal. Calcd for $C_{28}H_{26}N_2O_4$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.03; H, 6.04; N, 6.09. HPLC $\tau_{(R,S)\text{-}\mathbf{10}}$ 10.0 min, $\tau_{(S,S)\text{-}\mathbf{10}}$ 11.7 min. ^{1}H NMR (400 MHz; DMSO-d_6, 100 °C) [*S*,*S*/*R*,*S* ratio 85:15]: δ 0.98 (0.45H, d, *J* 6.7, Me-*R*,*S*), 1.03 (2.55H, d, *J* 6.7, Me-*S*,*S*), 1.14 (0.15H, m, H^B-3-*R*,*S*), 1.29 (0.85H, dddd, *J* 13.0, 10.5, 7.1 and 5.0, H^B-3-*S*,*S*), 2.17–2.39 (1.3H, m, H^A-3-*S*,*S*, H^A-3-*R*,*S*, H^A-4- and H^B-4-*R*,*S*), 2.49 (overlapped by DMSO, m, H^B-4-*S*,*S*), 2.56 (0.85H, dd, *J* 14.1 and 4.2, H^B-3′-*S*,*S*), 2.68 (0.85H, dt, *J* 15.1 and 5.0, H^A-4-*S*,*S*), 3.12 (0.15H, dd, 14.3 and 9.5, H^B-3′-*R*,*S*), 3.48 (0.15H, dd, *J* 14.3 and 5.4, H^A-3′-*R*,*S*), 3.60 (2.55H, s, OMe-*S*,*S*), 3.63 (0.45H, s, OMe-*R*,*S*), 3.64 (0.85H, dd, *J* 14.1 and 11.6, H^A-3′-*R*, *S*), 4.57 (0.15H, m, H-2-*R*,*S*), 4.65 (0.85H, ddq, *J* 7.7, 7.1 and 6.7, H-2-*S*,*S*), 5.42 (0.15H, dd, *J* 9.5 and 5.4, H-2′-*R*,*S*), 5.72 (0.85H, dd, *J* 11.6 and 4.2, H-2′-*S*,*S*), 6.59 (1.7H, d, *J* 9.1, H-5′-*S*,*S*), 6.62 (1.7H, d, *J* 9.1, H-6′-*S*,*S*), 6.64–6.70 (0.45H, m, H-5 and H-6′-*R*,*S*), 6.78 (0.15H, td, *J* 7.5 and 1.5, H-6-*R*,*S*), 6.96–7.02 (0.45H, m, H-7- and H-5′-*R*,*S*), 7.18 (0.15H, d, *J* 7.9, H-8-*R*,*S*), 7.26–7.33 (1.7H, m, H-6- and H-5-*S*,*S*), 7.39 (0.85H, ddd, *J* 7.8, 7.0 and 1.6, H-7-*S*,*S*), 7.52–7.57 (1.15H, m, H-4″-*R*,*S* and H-8-*S*,*S*), 7.68 (0.3H, m, H-3″-*R*,*S*), 7.82 (3.4H, s, H-3″- and H-4″-*S*,*S*).

4.5.4. 2,3-Dihydro-3-methyl-4-[*O*-methyl-*N*-phthaloyl-(*S*)-tyrosyl]-4*H*-1,4-benzoxazine 11 (diastereoisomeric mixture)

Colourless solid (0.324 g, 71%): mp 74–79 °C. Anal. Calcd for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14. Found: C, 71.06; H, 5.48; N, 6.15. HPLC $\tau_{(R,S)\text{-}\mathbf{11}}$ 9.0 min, $\tau_{(S,S)\text{-}\mathbf{11}}$ 12.2 min. ^{1}H NMR (400 MHz; DMSO-d_6, 100 °C) [*S*,*S*/*R*,*S* ratio 78:22]: δ 0.87 (0.66H, d, *J* 6.8, Me-*R*,*S*), 1.08 (2.34H, d, *J* 6.8, Me-*S*,*S*), 3.16 (0.78H, dd, *J* 14.1 and 5.6, H^B-3′-*S*,*S*), 3.22 (0.22H, dd, *J* 14.1 and 9.6, H^B-3′-*R*,*S*), 3.44 (0.22H, dd, *J* 14.1 and 5.5, H^A-3′-*R*,*S*), 3.64 (2.34H, s, OMe-*S*,*S*), 3.65 s (0.66H, s, OMe-*R*,*S*), 3.66 (0.78H, dd, *J* 14.1 and 10.2, H^A-3′-*S*,*S*), 4.06 (0.78H, dd, *J* 11.0 and 3.2, H^B-2-*S*,*S*), 4.10 (0.44H, d, *J* 2.1, H-2-*R*,*S*), 4.18 (0.78H, dd, *J* 11.0 and 1.7, H^A-2-*S*,*S*), 4.51 (0.22H, m, H-3-*R*,*S*), 4.76 (0.78H, qdd, *J* 6.8, 3.2 and 1.7, H-3-*S*,*S*), 5.55 (0.22H, dd, *J* 9.6 and 5.5, H-2′-*R*,*S*), 5.71 (0.78H, dd, *J* 10.2 and 5.6, H-2′-*S*,*S*), 6.60 (0.22H, dd, *J* 8.1 and 1.5, H-8-*R*,*S*), 6.67–6.75 (2.22H, m, H-6′-*S*,*S*, H-6′-*R*,*S* and H-7-*R*,*S*), 6.83 (0.22H, ddd, *J* 8.1, 7.3 and 1.5, H-6-*R*,*S*), 6.90 (0.78H, dd, *J* 8.2 and 1.5, H-8-*S*,*S*), 6.93 (1.56H, d, *J* 8.8, H-5′-*S*,*S*), 6.97 (0.78H, ddd, *J* 8.1, 7.3 and 1.5, H-6-*S*,*S*), 7.05 (0.44H, d, *J* 8.6, H-5′-*R*,*S*), 7.12 (0.78H, ddd, *J* 8.2, 7.3 and 1.5, H-7-*S*,*S*), 7.43 (0.22H, dd, *J* 8.1 and 1.5, H-5-*R*,*S*), 7.68 (0.44H, m, H-4″-*R*,*S*), 7.72 (0.78H, dd, *J* 8.1 and 1.5, H-5-*S*,*S*), 7.74 (0.44H, m, H-3″-*R*,*S*), 7.82 (3.12H, s, H-3″- and H-4″-*S*,*S*).

4.6. (*S*,*S*)-Amides 8–11. General procedure

A solution of acyl chloride **4** or **5** (0.5 mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of amine (*S*)-**1** or (*S*)-**2** (1.0 mmol) in CH_2Cl_2 (5 mL) at +20 °C. The reaction mixture was stirred at +20 °C for 6 h and then washed with 1 M HCl (5 mL), brine (3 × 5 mL), saturated aqueous $NaHCO_3$ (5 mL), and water (3 × 5 mL). The organic layer was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (eluent benzene/EtOAc 96:4) and then treated with hexane.

4.6.1. (2*S*)-2-Methyl-1-[3-(4-nitrophenyl)-*N*-phthaloyl-(*S*)-alanyl]-1,2,3,4-tetrahydroquinoline (*S*,*S*)-8

Colourless powder (0.291 g, 62%): mp 141–143 °C. $[\alpha]_D^{20} = +383$ (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{27}H_{23}N_3O_5$: C, 69.07; H, 4.94; N, 8.95. Found: C, 68.82; H, 4.83; N, 8.87. HPLC: de 99.7% (τ 12.22 min). ^{1}H NMR (400 MHz; DMSO-d_6, 100 °C): δ 1.04 (3H, d, *J* = 6.6, Me), 1.30 (1H, dddd, *J* 13.1, 10.4, 6.9 and 5.1, H^B-3), 2.33 (1H, ddt, *J* 13.1, 7.6 and 5.2, H^A-3), 2.48 (overlapped by DMSO, m, H^B-4), 2.67 (1H, dt, *J* 15.1 and 5.1, H^A-4), 2.82 (1H, dd, *J* 14.3 and 4.7, H^B-3′), 3.85 (1H, dd, *J* 14.3 and 11.1, H^A-3′), 4.65 (1H, ddq, *J* 7.6, 6.8 and 6.6, H-2), 5.80 (1H, dd, *J* 11.1 and 4.7, H-2′), 7.00 (2H, d, *J* 8.8, H-5′), 7.25–7.30 (2H, m, H-5 and H-6), 7.38 (1H, m, H-7), 7.55 (1H, d, *J* 7.6, H-8), 7.83 (4H, s, H-3″ and H-4″), 7.92 (2H, d, *J* 8.8, H-6′). ^{13}C NMR (125 MHz; DMSO-d_6; 100 °C): δ 19.35 (Me), 24.79 (C4), 31.45 and 31.59 (C3, C3′), 48.98 (C2), 53.96 (C2′), 122.62 (C3″), 122.72 (C6′), 124.64 (C8), 125.96 (C6), 126.32 (C7), 127.55 (C5), 128.79 (C5′), 130.61 (C2″a), 134.18 (C4″), 135.43 (C4a), 135.83 (C8a), 144.47 (C4′), 146.13 (C7′), 166.41 (C1′), 167.46 (C2″).

4.6.2. (3*S*)-2,3-Dihydro-3-methyl-4-[3-(4-nitrophenyl)-*N*-phthaloyl-(*S*)-alanyl]-4*H*-1,4-benzoxazine (*S*,*S*)-9

Colourless powder (0.259 g, 55%): mp 106–108 °C. $[\alpha]_D^{20} = +339$ (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{26}H_{21}N_3O_6$: C, 66.24; H, 4.49; N, 8.91. Found: C, 66.26; H, 4.76; N, 8.63. HPLC: de $\geqslant$99.9% (τ 12.98 min). ^{1}H NMR (400 MHz; DMSO-d_6, 100 °C): δ 1.09 (3H, d, *J* 6.9, Me), 3.42 (1H, dd, *J* 14.2 and 6.1, H^B-3′), 3.85 (1H, dd, *J* 14.2 and 9.7, H^A-3′), 4.04 (1H, dd, *J* 11.0 and 3.3, H^B-2), 4.17 (1H, dd, *J* 11.0 and 1.7, H^A-2), 4.75 (1H, qdd, *J* 6.9, 3.3 and 1.7, H-3), 5.81 (1H, dd, *J* 9.7 and 6.1, H-2′), 6.85 (1H, dd, *J* 8.2 and 1.5, H-8), 6.96 (1H, ddd, *J* 8.2, 7.3 and 1.5, H-6), 7.10 (1H, ddd, *J* 8.2, 7.3 and 1.6, H-7), 7.35 (2H, d, *J* 8.5, H-5′), 7.75 (1H, dd, *J* 8.2 and 1.6, H-5), 7.83 (4H, s, H-3″ and H-4″), 7.98 (2H, d, *J* 8.5, H-6′). ^{13}C NMR (125 MHz; DMSO-d_6, 100 °C): δ 14.64 (Me), 33.14 (C3′), 45.30 (C3), 53.28 (C2′), 69.36 (C2), 116.16 (C8), 11 9.85 (C6), 122.69 (C3″), 122.76 (C4a), 124.19 (C5), 125.81 (C7), 129.37 (C5′), 130.53 (C2″a), 134.23 (C4″), 144.32 (C4′), 146.01 (C8a), 146.23 (C7′), 166.03 (C1′), 164.18 (C2″).

4.6.3. (2*S*)-2-Methyl-1-[*O*-methyl-*N*-phthaloyl-(*S*)-tyrosyl]-1,2,3,4-tetrahydroquinoline (*S*,*S*)-10

Colourless powder (0.318 g, 70%): mp 122 °C. $[\alpha]_D^{20} = +369$ (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{28}H_{26}N_2O_4$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.12; H, 6.03; N, 5.92. HPLC: de 99.7% (τ 11.68 min). ^{1}H NMR (400 MHz; DMSO-d_6, 100 °C): δ 1.03 (3H, d, *J* 6.7, Me), 1.29 (1H, dddd, *J* 13.0, 10.5, 7.1 and 5.0, H^B-3), 2.35 (1H, ddt, *J* 13.0, 7.7 and 5.0, H^A-3), 2.48 (overlapped by DMSO, m, H^B-4), 2.56 (1H, dd, *J* 14.1 and 4.2, H^B-3′), 2.68 (1H, dt, *J* 15.1 and 5.0, H^A-4), 3.60 (3H, s, OMe), 3.64 (1H, dd, *J* 14.1 and 11.6, H^A-3′), 4.65 (1H, ddq, *J* 7.7, 7.1 and 6.7, H-2), 5.71 (1H, dd, *J* 11.6 and 4.2, H-2′), 6.59 (2H, d, *J* 9.1, H5′), 6.62 (2H, d, *J* 9.1, H6′), 7.26–7.33 (2H, m, H-5 and H-6), 7.40 (1H, ddd, *J* 7.8, 7.0 and 1.5, H-7), 7.53 (1H, d, *J* 7.8, H-8), 7.82 (4H, s, H-3″ and H-4″). ^{13}C NMR (125 MHz; DMSO-d_6, 100 °C): δ 19.47 (Me), 24.90 (C4), 30.47 (C3′), 31.64 (C3), 48.84 (C2), 54.50 (OMe), 54.94 (C2′), 113.49 (C6′), 122.50 (C3″), 124.71 (C8), 125.89 (C6), 126.27 (C7), 127.48 (C5), 128.47 (C5′), 128.48 (C4′), 130.67 (C2″a), 134.08 (C4″), 135.58 (C4a), 136.07 (C8a), 157.60 (C7′), 166.98 (C1′), 167.52 (C2″).

4.6.4. (3*S*)-2,3-Dihydro-3-methyl-4-[*O*-methyl-*N*-phthaloyl-(*S*)-tyrosyl]-4*H*-1,4-benzoxazine (*S*,*S*)-11

Colourless powder (0.310 g, 68%): mp 79–80 °C. $[\alpha]_D^{20} = +305$ (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14. Found: C, 71.13; H, 5.43; N, 6.14. HPLC: de $\geqslant$99.9% (τ 12.13 min). ^{1}H NMR (400 MHz; DMSO-d_6, 100 °C): δ 1.08 (3H, d, *J* 6.7, Me), 3.16 (1H, dd, *J* 14.1 and 5.6, H^B-3′), 3.64 (3H, s, OMe), 3.66 (1H, dd, *J* 14.1 and 10.2, H^A-3′), 4.06 (1H, dd, *J* 11.0 and 3.3, H^B-2), 4.18 (1H, dd, *J* 11.0 and 1.7, H^A-2), 4.76 (1H, qdd, *J* 6.7, 3.2 and 1.7, H-3), 5.71 (1H, dd, *J* 10.2 and 5.6, H-2′), 6.70 (2H, d, *J* 8.8, H-6′), 6.90 (1H, dd, *J* 8.2 and 1.5, H-8), 6.93 (2H, d, *J* 8.8, H-5′), 6.98 (1H, ddd, *J* 8.1, 7.3 and 1.5, H-6), 7.12 (1H, ddd, *J* 8.2, 7.3 and 1.5, H-7), 7.72 (1H, dd, *J* 8.1 and 1.5, H-5), 7.82 (4H, s, H-3″ and H-4″). ^{13}C NMR (125 MHz; DMSO-d_6, 100 °C): δ 14.54 (Me), 32.02 (C3′), 45.30 (C3), 54.23 (C2′), 54.56 (OMe), 69.44 (C2), 113.55 (C6′), 116.21 (C8), 119.81 (C6), 122.56 (C3″), 122.88 (C4a), 124.25 (C5), 125.77 (C7), 128.20 (C4′), 128.96 (C5′), 130.61 (C2″a), 134.10 (C4″), 146.05 (C8a), 157.77 (C7′), 166.66 (C1′), 167.27 (C2″).

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