Convenient asymmetric synthesis of 1,3,4,6-tetrasubstituted 2,5-diketopiperazines

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Abstract

A general and efficient method was developed for the asymmetric synthesis of 1,3,4,6-tetrasubstituted 2,5-diketopiperazines. The asymmetric nucleophilic substitution of L-amino acid-derived α-bromo tertiary amides with aliphatic primary amines followed by spontaneous cyclization provides a rapid access to diverse 1,3,4,6-tetrasubstituted-2,5-diketopiperazines with high diastereoselectivities of up to 99:1 dr.

Keywords: Nucleophilic substitution, amino acid, chirality, peptidomimetics, asymmetric synthesis

Introduction

2,5-Diketopiperazines with four substituents at the 1,3,4 and 6 positions are interesting scaffolds for drug design and peptide chemistry, because the substituents of the rigid cyclic dipeptide can be arranged in a well-defined spatial manner.[1-2] Among them, special attention has been paid to unsymmetrical tetra-substituted diketopiperazines which can provide a unique opportunity to design suitable drug candidates.[3-6] (Figure 1) Thus, asymmetric synthetic methods for unsymmetrical tetrasubstituted diketopiperazines are highly desirable. However, the synthetic methods involving naturally occurring L-amino acids are often limited by the diversity of the substituents. Furthermore, the syntheses of tetrasubstituted diketopiperazines require either multistep sequences or harsh conditions and they are inefficient for asymmetric synthesis.[7-13] As an extension of our previous work on the asymmetric preparation of 3,4,6-trisubstituted 2,5-diketopiperazines,[14] we herein report a mild and versatile synthetic method for the asymmetric synthesis of 1,3,4,6-tetrasubstituted 2,5-diketopiperazines via one-pot substitution-cyclization of α-bromo tertiary acetamides (Figure 1).

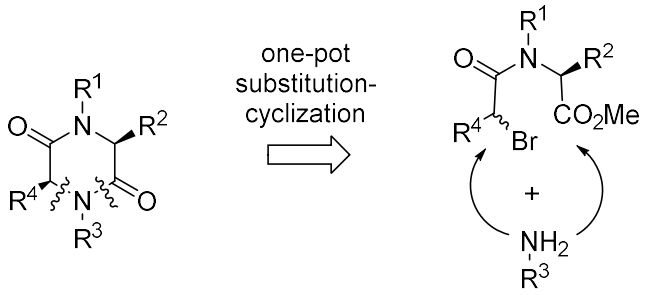


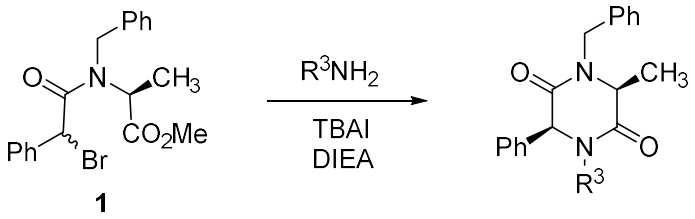
Figure 1. Retrosynthesis of unsymmetrical 1,3,4,6-tetrasubstituted 2,5-diketopiperazines ($R^1 \neq R^3$ and $R^2 \neq R^4$).

Results and Discussion

We previously reported that the dynamic kinetic resolution of L-amino acid-derived α-bromo tertiary acetamides in nucleophilic substitution with *p*-anisidine affords highly diastereoenriched dipeptide analogs and subsequent deprotection-cyclization process gives 3,4,6-trisubstituted 2,5-diketopiperazines.[14] In our efforts to extend the synthetic method to the asymmetric synthesis of tetrasubstituted 2,5-diketopiperazines, we have found a simple and convenient synthetic method involving the substitution and spontaneous cyclization with primary aliphatic amines.

In contrast to the reaction of α-bromo tertiary acetamide **1** with *p*-anisidine, the substitution of **1** with benzylamine spontaneously afforded a cyclized product **2** under the same conditions (Table 1, entries 1 and 2). The tetrasubstituted 2,5-diketopiperazine was produced in 88% yield and with 98:2 dr after 48 h stirring with DIEA and TBAI in CH_3CN by the dynamic kinetic resolution of α-bromo tertiary acetamide **1** (50:50 dr).[15-20] Next, several primary amine nucleophiles were screened as shown in Table 1; most of the primary amines successfully afforded tetrasubstituted 2,5-diketopiperazines. The reactions of **1** with *n*-propylamine, *n*-butylamine, *iso*-butylamine, 2-phenethylamine and methylamine (2.0 M solution in THF) afforded diketopiperazines **3**-**7** in yields ranging from 51% to 88% and with comparably high stereoselectivities, as shown in entries 3-7. More sterically demanding isopropylamine afforded a substitution product, but no cyclization occurred under the same reaction conditions (entry 8). The synthetic method was extended to functionalized amine nucleophiles to obtain diverse diketopiperazines with additional functionalities. The reactions of **1** with amines containing methoxycarbonylmethyl, *N*-Boc-aminoethyl, indol-3-ylethyl and *p*-methoxybenzyl groups also afforded highly diastereoenriched diketopiperazines **8**-**11** with 96:4, 96:4, 95:5 and 96:4 drs, respectively (entries 9-12).

Table 1. Synthesis of tetrasubstituted 2,5-diketopiperazines using alkyl amines

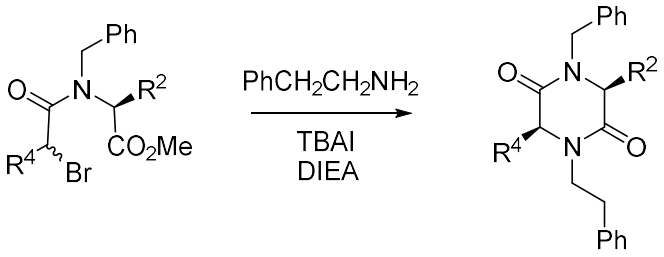


Entry[a]	R^3	Dr (α*S*:α*R*)[b]	Product	Yield (%)[c]
1	*p*-$MeOC_6H_4$	-	**-**	-
2	$PhCH_2$	98:2	**2**	88
3	$CH_3CH_2CH_2$	95:5	**3**	88
4	$CH_3CH_2CH_2CH_2$	95:5	**4**	72
5	$(CH_3)_2CHCH_2$	96:4	**5**	66
6	$PhCH_2CH_2$	94:6	**6**	75
7	CH_3	96:4	**7**	51
8	$(CH_3)_2CH$	-	**-**	-
9	MeO_2CCH_2	96:4	**8**	76
10	$BocNHCH_2CH_2$	96:4	**9**	60
11	(indol-3-yl)CH_2CH_2	95:5	**10**	83
12	*p*-$MeOC_6H_4CH_2$	96:4	**11**	77

[a] All the reactions were carried out in CH_3CN at rt for 48 h. [b] The drs were determined by the ^1H NMR spectra of the reaction mixtures. [c] Isolated yields.

To establish the generality of the synthetic methodology, the substrate scope of the stereoselective diketopiperazine formation was investigated using four different L-amino acid precursors (Table 2). The substitution reactions of *N*-benzyl substituted α-bromo acetamides **12-15** derived from L-phenylalanine, L-leucine, L-aspartic acid, and L-glutamic acid were studied as shown in entries 1-4. The reaction of L-Phe-derived α-bromo acetamide **12** with 2-phenylethylamine, TBAI and DIEA afforded diketopiperazine **20** with 96:4 dr (entry 1). Almost the same selectivities were observed with L-Leu, L-Asp, and L-Glu-derived α-bromo acetamides **13-15** (entries 2-4). Next, the effect of R^4 substituents on the stereoselectivity of the substitution was studied (entries 5-8). Two aromatic and two aliphatic substituents (R^2) such as *p*-chlorophenyl, *p*-bromophenyl, methyl and ethyl groups were investigated. The reactions of α-bromo acetamides **16** and **17** with 2-phenylethylamine, TBAI and DIEA afforded the corresponding products with a slightly lower drs of 92:8 and 93:7, respectively. The reactions of α-bromo acetamides **18** and **19** bearing aliphatic R^4 substituents showed much lower selectivities of 87:13 and 90:10 drs, respectively, under identical reaction conditions.

Table 2. Synthesis of tetrasubstituted 2,5-diketopiperazines with different R^2 and R^4 substituents



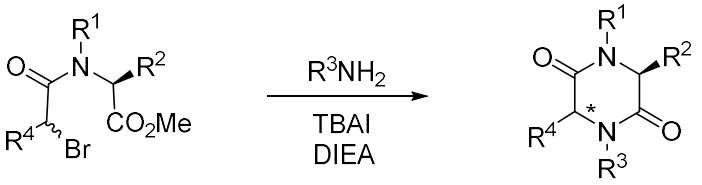
Entry[a]	Reactant	R^2	R^4	Dr (αS:αR)[b]	Product	Yield (%)[c]
1	**12**	$PhCH_2$	Ph	96:4	**20**	56
2	**13**	$(CH_3)_2CHCH_2$	Ph	97:3	**21**	70
3	**14**	MeO_2CCH_2	Ph	97:3	**22**	71
4	**15**	$MeO_2CCH_2CH_2$	Ph	94:6	**23**	81
5	**16**	$(CH_3)_2CHCH_2$	*p*-ClC_6H_4	92:8	**24**	48
6	**17**	$(CH_3)_2CHCH_2$	*p*-BrC_6H_4	93:7	**25**	51
7	**18**	$(CH_3)_2CHCH_2$	CH_3	87:13	**26**	89
8	**19**	$(CH_3)_2CHCH_2$	CH_3CH_2	90:10	**27**	75

[a] All the reactions were carried out in CH_3CN at rt for 48 h. [b] The drs were determined by the H NMR spectra of the reaction mixtures. [c] Isolated yields.

Encouraged by the observed high stereoselectivity in the reaction of *N*-benzyl substituted α-bromo acetamides with primary amines, *N*-(*p*-methoxybenzyl) substituted α-bromo acetamides **28-30** were investigated. *N*-(*p*-methoxybenzyl) group can be used for the temporary protection of the tertiary amide bond, affording an *N*-unsubstituted 2,5-diketopiperazine.[21-22] The reactions of L-leucine-derived **28** and L-alanine-derived **29** with benzylamine afforded *N*-(*p*-methoxybenzyl) substituted diketopiperazines **35** and **36** in good yields and with excellent drs of 98:2 and 99:1, respectively (entries 1 and 2). The reactions of **29** with *n*-propylamine and *p*-methoxybenzylamine afforded highly diastereoenriched **37** and **38**, respectively (entries 3 and 4). We were pleased to observe that **30** bearing an aliphatic methyl substituent (R^4) also afforded a tetrasubstituted 2,5-diketopiperazine **39** with 99:1 dr. We confirmed the *cis* configuration of diketopiperazines **38** and **39** by comparing their NMR spectra with those of previously reported compounds.[23-26] The reactions of *N*-(*trans*-cinnamyl) substituted α-bromo acetamides **31** and **32** produced highly functionalized diketopiperazines **40** and **41** with stereoselectivities of 99:1 and 92:8 dr, respectively. Finally, this methodology was found to be efficient for the synthesis of L-proline-derived diketopiperazines with high stereoselectivities and good yields as shown in entries 8-10. The reactions of L-proline-derived α-bromo phenylacetamide **33** with 2-

phenylethylamine and *p*-methoxybenzylamine afforded the corresponding *trans*-diketopiperazines **42** and **43** with 93:7 and 96:4 drs, respectively. However, a much lower stereoselectivity of 75:25 dr was observed in the reactions of L-proline-derived α-bromo propionamide **34** bearing an aliphatic R^4 substituent, affording *trans*-diketopiperazine **44** in 76% yield (entry 10).[25-26]

Table 3. Stereoselective synthesis of 1,3,4,6-tetrasubstituted 2,5-diketopiperazines



Entry[a]	R^1	R^2	R^3	R^4	Dr (α*S*:α*R*)[b]	Product	Yield (%)[c]
1 (**28**)	*p*-$MeOC_6H_4CH_2$	$(CH_3)_2CHCH_2$	$PhCH_2$	Ph	98:2	**35**	70
2 (**29**)	*p*-$MeOC_6H_4CH_2$	CH_3	$PhCH_2$	Ph	99:1	**36**	73
3 (**29**)	*p*-$MeOC_6H_4CH_2$	CH_3	$CH_3CH_2CH_2$	Ph	99:1	**37**	80
4 (**29**)	*p*-$MeOC_6H_4CH_2$	CH_3	*p*-$MeOC_6H_4CH_2$	Ph	96:4	**38**	68
5 (**30**)	*p*-$MeOC_6H_4CH_2$	CH_3	*p*-$MeOC_6H_4CH_2$	CH_3	99:1	**39**	60
6 (**31**)	$PhCH=CHCH_2$	$(CH_3)_2CHCH_2$	$PhCH_2CH_2$	Ph	99:1	**40**	56
7 (**32**)	$PhCH=CHCH_2$	CH_3	*p*-$MeOC_6H_4CH_2$	Ph	92:8	**41**	77
8 (**33**)	-$CH_2CH_2CH_2$-		$PhCH_2CH_2$	Ph	7:93	**42**	66
9 (**33**)	-$CH_2CH_2CH_2$-		*p*-$MeOC_6H_4CH_2$	Ph	4:96	**43**	87
10 (**34**)	-$CH_2CH_2CH_2$-		*p*-$MeOC_6H_4CH_2$	CH_3	25:75	**44**	76

[a] All the reactions were carried out in CH_3CN at rt for 48 h. Numbers in parentheses after entry numbers indicate reactant numbers. [b] The drs were determined by the H NMR spectra of the reaction mixtures. [c] Isolated yields.

Conclusions

A mild one-pot synthetic method was developed for the asymmetric synthesis of 1,3,4,5-tetrasubstituted 2,5-diketopiperazines. The highly stereoselective process includes the dynamic kinetic resolution of α-bromo tertiary amides in asymmetric substitution with a primary aliphatic amine as the key reaction. The following spontaneous cyclization provides 1,3,4,6-tetrasubstituted 2,5-diketopiperazines. The asymmetric synthetic methodology provides a rapid

access to diverse highly functionalized diketopiperazines. By the introduction of appropriate substituents in four defined positions, the diketopiperazines could be used as scaffolds for further functionalization in the asymmetric synthesis of complex target molecules.

Experimental Section

General. All reactions were performed in oven-dried glassware under nitrogen atmosphere. All chemicals were obtained from commercial sources and were used as received. Analytical thin layer chromatography (TLC) was performed on silica gel plates with QF-254 indicator and TLC visualization was carried out with UV-light. Flash column chromatography was performed with 230–400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were acquired on Bruker (400 MHz ^{1}H, 100.6 MHz ^{13}C) spectrometer using chloroform-*d* ($CDCl_3$) as the internal standard. Chemical shifts (δ) are reported in ppm relative to chloroform-*d* (7.26 ppm ^{1}H, 77.07 ppm ^{13}C). Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet) and br (broad). Coupling constants (*J*) are reported in Hz. HRMS spectra were measured on a JEOL JMS-700 by using ESI or FAB method.

General procedure for the preparation of 1,3,4,6-tetrasubstituted 2,5-diketopiperazines. To a solution of L-amino acid-derived (*αRS*)-α-bromo tertiary acetamide (1.0 mmol) in dry CH_3CN (≈ 0.1 M of substrate) at room temperature was added an amine (1.2 equiv), TBAI (1.0 equiv) and DIEA (1.0 equiv). The resulting reaction mixture was stirred at room temperature for 48 h before the solvent was evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel to give 1,3,4,6-tetrasubstituted 2,5-diketopiperazines. The purity (>95 %) of products was estimated by NMR spectroscopy.

(3*S*,6*S*)-1,4-Dibenzyl-6-methyl-3-phenylpiperazine-2,5-dione (2) A colorless oil was obtained in 88% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.45-7.14 (m, 15H), 5.59 (d, *J* 14.8 Hz, 1H), 5.12 (d, *J* 14.8 Hz, 1H), 5.10 (s, 1H), 4.07 (q, *J* 6.8 Hz, 1H), 3.96 (d, *J* 14.8 Hz, 1H), 3.59 (d, *J* 14.4 Hz, 1H), 1.45 (d, *J* 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 168.0, 164.8, 135.7, 135.6, 135.2, 135.1, 129.1, 129.0, 128.9, 128.7, 128.4, 128.2, 128.0, 126.6, 62.4, 55.2, 47.6, 47.4, 19.1; HRMS calcd for $C_{25}H_{24}N_2O_2$ (M^+): 384.1838. Found 384.1839.

(3*S*,6*S*)-1-Benzyl-6-methyl-3-phenyl-4-*n*-propylpiperazine-2,5-dione (3) A colorless oil was obtained in 88% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.46-7.20 (m, 10H), 5.23 (s, 1H), 5.17 (d, *J* 14.8 Hz, 1H), 4.09-3.93 (m, 3H), 2.66-2.59 (m, 1H), 1.64-1.55 (m, 2H), 1.37 (d, *J* 6.8 Hz, 3H), 0.88 (t, *J* 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 168.0, 165.0, 135.6, 135.5, 129.0, 128.9, 128.6, 128.1, 128.0, 126.4, 63.4, 55.1, 47.3, 47.0, 20.4, 18.7, 11.2; HRMS calcd for $C_{21}H_{24}N_2O_2$ (M^+): 336.1838. Found 336.1836.

(3*S*,6*S*)-1-Benzyl-4-*n*-butyl-6-methyl-3-phenylpiperazine-2,5-dione (4) A colorless oil was obtained in 72% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.46-7.20 (m, 10H), 5.23 (s, 1H), 5.15 (d, *J* 15.2 Hz, 1H), 4.14-3.94 (m, 3H), 2.67-2.60 (m, 1H), 1.58-1.54 (m, 2H), 1.36 (d, *J* 6.8 Hz, 3H),

1.33-1.26 (m, 2H), 0.90 (t, *J* 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.9, 165.1, 135.6, 135.5, 129.0, 128.9, 128.6, 128.1, 128.0, 126.4, 63.4, 55.2, 47.3, 45.3, 29.2, 20.0, 18.7, 13.7; HRMS calcd for $C_{22}H_{26}N_2O_2$ (M^+): 350.1994. Found 350.1991.

(3*S*,6*S*)-1-Benzyl-4-isobutyl-6-methyl-3-phenylpiperazine-2,5-dione (5) A colorless oil was obtained in 66% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.46-7.15 (m, 14H), 5.25 (s, 1H), 5.20 (d, *J* 14.8 Hz, 1H), 4.11-3.91 (m, 3H), 2.43-2.31 (m, 1H), 2.10-1.99 (m, 1H), 1.34 (d, 1H), 0.95-0.84 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 168.6, 165.1, 135.7, 135.5, 129.0, 128.9, 128.5, 127.9, 127.8, 126.2, 64.0, 55.1, 52.5, 47.2, 26.5, 20.1, 19.8, 18.4; HRMS calcd for $C_{22}H_{26}N_2O_2$ (M^+): 350.1994. Found 350.1992.

(3*S*,6*S*)-1-Benzyl-6-methyl-4-(2-phenylethyl)-3-phenylpiperazine-2,5-dione (6) A colorless oil was obtained in 75% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.38-7.11 (m, 15H), 5.22 (d, *J* 15.2 Hz, 1H), 4.88 (s, 1H), 4.35-4.30 (m, 1H), 3.95 (q, *J* 6.8 Hz, 1H), 3.83 (d, *J* 15.2 Hz, 1H), 2.95-2.77 (m, 3H), 1.37 (d, *J* 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.9, 164.7, 138.1, 135.6, 129.2, 129.0, 128.9, 128.8, 128.7, 128.6, 128.1, 127.2, 126.8, 126.4, 64.3, 54.8, 47.5, 47.1, 33.5, 18.6; HRMS calcd for $C_{26}H_{26}N_2O_2$ (M^+): 398.1994. Found 398.1995.

(3*S*,6*S*)-1-Benzyl-4,6-dimethyl-3-phenylpiperazine-2,5-dione (7) A pale yellow oil was obtained in 51% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.42-7.22 (m, 10H), 5.19 (d, *J* 14.8 Hz, 1H), 5.13 (s, 1H), 4.00 (q, *J* 7.2 Hz, 1H), 3.90 (d, *J* 14.8 Hz, 1H), 2.96 (s, 3H), 1.43 (d, *J* 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.9, 164.6, 135.6, 135.2, 129.1, 128.9, 128.6, 128.3, 128.0, 126.3, 65.9, 54.9, 47.2, 33.1, 19.0; HRMS calcd for $C_{19}H_{21}N_2O_2$ (M^++1): 309.1603. Found 309.1603.

(3*S*,6*S*)-1-Benzyl-4-methoxycarbonylmethyl-6-methyl-3-phenyl piperazine-2,5-dione (8) A colorless oil was obtained in 76% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.46-7.22 (m, 10H), 5.30 (s, 1H), 5.18 (d, *J* 15.2 Hz, 1H), 4.78 (d, *J* 17.6 Hz, 1H), 4.07-4.00 (m, 2H), 3.70 (s, 3H), 3.42 (d, *J* 17.6 Hz, 1H), 1.44 (d, *J* 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 168.3, 168.0, 164.3, 135.4, 134.8, 129.2, 129.0, 128.9, 128.1, 128.0, 126.6, 64.7, 54.8, 52.5, 47.4, 46.1, 19.3; HRMS calcd for $C_{21}H_{22}N_2O_4$ (M^+): 366.1580. Found 366.1579.

(3*S*,6*S*)-4-(*N*-Boc-2-aminoethyl)-1-benzyl-6-methyl-3-phenyl piperazine-2,5-dione (9) A colorless oil was obtained in 60% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.42-7.22 (m, 10H), 5.29 (s, 1H), 5.11 (d, *J* 15.2 Hz, 1H), 4.97 (br, 1H), 4.08-3.98 (m, 3H), 3.33-3.30 (m, 1H), 2.94-2.88 (m, 1H), 1.43-1.36 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) 168.6, 164.6, 156.0, 135.6, 135.4, 129.1, 128.9, 128.2, 128.0, 126.4, 79.6, 64.6, 55.1, 47.4, 45.7, 38.7, 28.4, 18.9; HRMS calcd for $C_{25}H_{32}N_3O_4$ (M^++1): 438.2393. Found 438.2388.

(3*S*,6*S*)-1-Benzyl-4-(3-indoleethyl)-6-methyl-3-phenylpiperazine-2,5-dione (10) A pale yellow oil was obtained in 83% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.40 (br, 1H), 7.54-6.84 (m, 15H), 5.09 (d, *J* 14.8 Hz, 1H), 4.99 (s, 1H), 4.37-4.31 (m, 1H), 3.99 (q, *J* 7.2 Hz, 1H), 3.91 (d, *J* 14.8 Hz, 1H), 3.13-2.88 (m, 3H), 1.38 (d, *J* 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.9, 164.9, 136.3, 135.7, 135.6, 129.0, 128.9, 128.6, 128.3, 128.1, 127.1, 126.5, 122.2, 122.1, 119.5, 118.5, 112.0, 111.5, 64.4, 55.2, 47.4, 46.8, 23.2, 18.8; HRMS calcd for $C_{28}H_{27}N_3O_2$ (M^+): 437.2103. Found 437.2103.

(3*S*,6*S*)-1-Benzyl-4-(4-methoxybenzyl)-6-methyl-3-phenylpiperazine-2,5-dione (11) A pale yellow oil was obtained in 77% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.45-6.82 (m, 14H), 5.52 (d, *J* 14.8 Hz, 1H), 5.10 (d, *J* 15.2 Hz, 1H), 5.08 (s, 1H), 4.05 (q, *J* 6.8 Hz, 1H), 3.96 (d, *J* 15.2 Hz, 1H), 3.77 (s, 3H), 3.53 (d, *J* 14.8 Hz, 1H), 1.44 (d, *J* 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.9, 164.9, 159.5, 135.7, 135.2, 129.9, 129.1, 128.9, 128.6, 128.0, 127.9, 127.2, 126.6, 114.3, 62.0, 55.3, 55.2, 47.3, 47.0, 19.1; HRMS calcd for $C_{26}H_{26}N_2O_3$ (M^+): 414.1943. Found 414.1942.

(3*S*,6*S*)-1,6-Dibenzyl-4-(2-phenylethyl)-3-phenylpiperazine-2,5-dione (20) A colorless oil was obtained in 56% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.26-6.92 (m, 20H), 5.20 (d, *J* 14.8 Hz, 1H), 4.71 (s, 1H), 4.17-4.05 (m, 2H), 3.15-3.09 (m, 2H), 2.88-2.61 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 166.4, 165.1, 138.2, 136.5, 135.5, 135.4, 129.7, 129.0, 128.9, 128.8, 128.7, 128.5, 128.4, 128.1, 127.4, 126.9, 126.6, 64.5, 60.5, 47.7, 47.6, 39.2, 33.4; HRMS: calcd. for $C_{32}H_{31}N_2O_2$ (M^++1) 475.2386; Found 475.2386.

(3*S*,6*S*)-1-Benzyl-6-isobutyl-4-(2-phenylethyl)-3-phenylpiperazine-2,5-dione (21) A colorless oil was obtained in 70% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.38-7.12 (m, 15H), 5.26 (d, *J* 14.8 Hz, 1H), 4.90 (s, 1H), 4.39-4.34 (m, 1H), 3.89-3.85 (m, 1H), 3.74 (d, *J* 14.8 Hz, 1H), 2.95-2.80 (m, 3H), 1.91-1.86 (m, 1H), 1.48-1.27 (m, 2H), 0.89 (d, *J* 6.4 Hz, 3H), 0.82 (d, *J* 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.3, 165.3, 138.1, 135.8, 135.3, 129.0, 128.9, 128.8, 128.7, 128.5, 128.2, 128.1, 126.8, 126.1, 64.2, 57.3, 47.8, 47.6, 42.5, 33.5, 25.0, 23.2, 21.5; HRMS: calcd. for $C_{29}H_{33}N_2O_2$ (M^++1) 441.2542; Found 441.2542.

(3*S*,6*S*)-1-Benzyl-6-methoxycarbonylmethyl-4-(2-phenylethyl)-3-phenylpiperazine-2,5-dione (22) A pale yellow oil was obtained in 71% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.39-7.09 (m, 15H), 5.09 (d, *J* 14.8 Hz, 1H), 4.86 (s, 1H), 4.50 (t, *J* 6.0 Hz, 1H), 4.37-4.25 (m, 1H), 3.98 (d, *J* 14.8 Hz, 1H), 3.65 (s, 3H), 2.97-2.72 (m, 4H), 2.51-2.46 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 170.4, 166.3, 164.9, 138.0, 135.7, 135.2, 129.2, 128.9, 128.8, 128.7, 128.2, 128.0, 126.9, 126.3, 64.3, 56.2, 52.3, 47.7, 38.9, 33.5; HRMS calcd for $C_{28}H_{29}N_2O_4$ (M^++1): 457.2127. Found 457.2123.

(3*S*,6*S*)-1-Benzyl-6-(2-methoxycarbonylethyl)-4-(2-phenylethyl)-3-phenylpiperazine-2,5-dione (23) A colorless oil was obtained in 81% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.40-7.23 (m, 15H), 5.23 (d, *J* 14.8 Hz, 1H), 4.85 (s, 1H), 4.52-4.27 (m, 2H), 3.98-3.77 (m, 2H), 3.67 (s, 3H), 2.95-2.38 (m, 5H), 2.09-2.06 (m, 1H), 1.73-1.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.9, 166.5, 164.8, 138.0, 135.8, 135.2, 130.0, 129.0, 128.9, 128.7, 128.6, 128.5, 128.0, 126.8, 126.1, 64.2, 57.8, 51.8, 47.7, 47.3, 33.4, 29.8, 27.4; HRMS: calcd. for $C_{29}H_{31}N_2O_4$ (M^++1) 471.2284; Found 471.2284.

(3*S*,6*S*)-1-Benzyl-3-(4-chlorophenyl)-6-isobutyl-4-(2-phenylethyl) piperazine-2,5-dione (24) A pale yellow oil was obtained in 48% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.39-7.11 (m, 14H), 5.24 (d, *J* 14.8 Hz, 1H), 4.82 (s, 1H), 4.39-4.32 (m, 1H), 3.89-3.85 (m, 1H), 3.76 (d, *J* 14.8 Hz, 1H), 2.98-2.74 (m, 3H), 1.91-1.84 (m, 1H), 1.44-1.25 (m, 2H), 0.88 (d, *J* 6.4 Hz, 3H), 0.80 (d, *J* 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.1, 164.9, 138.0, 135.6, 134.6, 133.8, 129.1, 129.0, 128.8, 128.7, 128.2, 128.1, 127.5, 126.9, 63.7, 57.3, 47.7, 47.6, 42.7, 33.5, 25.0, 23.1, 21.5; HRMS: calcd. for $C_{29}H_{32}ClN_2O_2$ (M^++1) 475.2152; Found 475.2152.

(3*S*,6*S*)-1-Benzyl-3-(4-bromophenyl)-6-isobutyl-4-(2-phenylethyl) piperazine-2,5-dione (25) A colorless oil was obtained in 51% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.51-7.08 (m, 14H), 5.23 (d, *J* 14.8 Hz, 1H), 4.80 (s, 1H), 4.37-4.32 (m, 1H), 3.89-3.85 (m, 1H), 3.76 (d, *J* 14.8 Hz, 1H), 2.96-2.76 (m, 3H), 1.89-1.86 (m, 1H), 1.41-1.32 (m, 2H), 0.90 (d, *J* 6.4 Hz, 3H), 0.82 (d, *J* 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.1, 164.8, 138.0, 135.6, 134.4, 132.0, 129.0, 128.8, 128.7, 128.2, 128.1, 127.9, 126.9, 122.7, 63.8, 57.3, 47.7, 47.6, 42.7, 33.5, 25.0, 23.2, 21.5; HRMS: calcd. for $C_{29}H_{32}BrN_2O_2$ (M^++1) 519.1647; Found 519.1647.

(3*S*,6*S*)-1-Benzyl-6-isobutyl-3-methyl-4-(2-phenylethyl)piperazine-2,5-dione (26) A colorless oil was obtained in 89% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.37-7.15 (m, 10H), 5.33 (d, *J* 14.8 Hz, 1H), 4.02-3.96 (m, 1H), 3.83-3.75 (m, 3H), 3.11-3.04 (m, 1H), 2.94-2.86 (m, 2H), 1.91-1.89 (m, 1H), 1.71-1.55 (m, 2H), 1.48 (d, *J* 7.2 Hz, 3H), 0.95-0.92 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.4, 166.3, 138.3, 135.7, 128.9, 128.8, 128.7, 128.2, 128.0, 126.7, 56.9, 47.1, 46.7, 43.3, 33.4, 25.1, 23.4, 21.7, 19.4; HRMS: calcd. for $C_{24}H_{31}N_2O_2$ (M^++1) 379.2386; Found 379.2386.

(3*S*,6*S*)-1-Benzyl-3-ethyl-6-isobutyl-4-(2-phenylethyl)piperazine-2,5-dione (27) A pale yellow oil was obtained in 75% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.35-7.14 (m, 10H), 5.30 (d, *J* 14.8 Hz, 1H), 4.11-4.05 (m, 1H), 3.80 (d, *J* 14.8 Hz, 1H), 3.80-3.77 (m, 1H), 3.65-3.61 (m, 1H), 3.06-2.81 (m, 3H), 1.98-1.69 (m, 4H), 1.57-1.50 (m, 1H), 1.06 (t, *J* 7.2 Hz, 3H), 0.94-0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 166.7, 166.3, 138.3, 135.9, 128.9, 128.7, 128.6, 128.2, 128.0, 126.7, 62.4, 57.1, 47.3, 47.0, 43.8, 33.4, 27.4, 25.5, 23.3, 21.7, 11.1; HRMS: calcd. for $C_{25}H_{33}N_2O_2$ (M^++1) 393.2542; Found 393.2543.

(3*S*,6*S*)-4-Benzyl-6-isobutyl-1-(4-methoxybenzyl)-3-phenyl piperazine-2,5-dione (35) A colorless oil was obtained in 70% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.47-6.83 (m, 14H), 5.61 (d, *J* 14.8 Hz, 1H), 5.20 (d, *J* 14.8 Hz, 1H), 5.12 (s, 1H), 3.98-3.95 (m, 1H), 3.81 (s, 3H), 3.76 (d, *J* 14.8 Hz, 1H), 3.61 (d, *J* 14.8 Hz, 1H), 1.96-1.90 (m, 1H), 1.62-1.51 (m, 1H), 1.41-1.34 (m, 1H), 0.92 (d, *J* 6.4 Hz, 3H), 0.85 (d, *J* 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.5, 165.5, 159.4, 135.5, 134.9, 129.4, 129.0, 128.9, 128.5, 128.2, 128.1, 127.7, 126.3, 114.3, 62.4, 57.3, 55.3, 47.8, 47.2, 42.8, 25.0, 23.1, 21.6; HRMS calcd for $C_{29}H_{32}N_2O_3$ (M^+): 456.2413. Found 456.2415.

(3*S*,6*S*)-4-Benzyl-1-(4-methoxybenzyl)-6-methyl-3-phenylpiperazine-2,5-dione (36) A colorless oil was obtained in 73% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.45-7.25 (m, 8H), 7.15-7.11 (m, 4H), 6.84-6.82 (m, 2H), 5.58 (d, *J* 14.8 Hz, 1H), 5.08 (d, *J* 14.8 Hz, 1H), 5.07 (s, 1H), 4.06 (q, *J* 7.2 Hz, 1H), 3.89 (d, *J* 14.8 Hz, 1H), 3.78 (s, 3H), 3.59 (d, *J* 14.8 Hz, 1H), 1.45 (d, *J* 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 168.1, 164.7, 159.4, 135.2, 135.1, 129.5, 129.1, 128.9, 128.7, 128.4, 128.1, 127.6, 126.6, 114.3, 62.4, 55.3, 54.9, 47.6, 46.8, 19.1; HRMS: calcd. for $C_{26}H_{27}N_2O_3$ (M^++1) 415.2022; Found 415.2022.

(3*S*,6*S*)-6-Methyl-1-(4-methoxybenzyl)-3-phenyl-4-(*n*-propyl) piperazine-2,5-dione (37) A colorless oil was obtained in 80% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.45-6.82 (m, 9H), 5.20 (s, 1H), 5.10 (d, *J* 14.8 Hz, 1H), 4.07-3.92 (m, 2H), 3.87 (d, *J* 14.8 Hz, 1H), 3.75 (s, 3H), 2.65-2.58 (m, 1H), 1.64-1.53 (m, 2H), 1.36 (d, *J* 6.8 Hz, 3H), 0.87 (t, *J* 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100

MHz) 167.9, 164.8, 159.3, 135.6, 129.6, 128.9, 128.5, 127.6, 126.3, 114.2, 63.4, 55.2, 54.8, 46.9, 46.6, 20.4, 18.6, 11.2; HRMS: calcd. for $C_{22}H_{27}N_2O_3$ (M^++1) 367.2022; found 367.2022**.**

(3*S*,6*S*)-1,4-Di(4-methoxybenzyl)-6-methyl-3-phenylpiperazine-2,5-dione (38) A colorless oil was obtained in 68% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.45-7.25 (m, 5H), 7.11-7.05 (m, 4H), 6.84-6.80 (m, 4H), 5.50 (d, *J* 14.4 Hz, 1H), 5.07 (s, 1H), 5.03 (d, *J* 14.8 Hz, 1H), 4.05 (q, *J* 7.2 Hz, 1H), 3.89 (d, *J* 14.8 Hz, 1H), 3.74-3.71 (m, 6H), 3.53 (d, *J* 14.8 Hz, 1H), 1.44 (d, *J* 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.9, 164.7, 159.5, 135.2, 129.9, 129.5, 129.1, 129.0, 128.6, 127.7, 127.3, 127.2, 126.6, 114.3, 114.2, 62.1, 55.3, 55.2, 54.9, 47.0, 46.7, 19.1; HRMS calcd for $C_{27}H_{28}N_2O_4$ (M^+): 444.2049. Found 444.2047.

(3*S*,6*S*)-1,4-Di(4-methoxybenzyl)-3,6-dimethylpiperazine-2,5-dione (39) A colorless oil was obtained in 60% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.15 (d, *J* 8.4 Hz, 4H), 6.85 (d, *J* 8.4 Hz, 4H), 5.08 (d, *J* 14.8 Hz, 2H), 4.02-3.93 (m, 4H), 3.79 (s, 6H), 1.49 (d, *J* 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.1, 159.4, 129.6, 127.8, 114.6, 55.3, 54.9, 46.6, 19.1. The spectral data of **39** were identical to those of the authentic material reported previously.[26]

(3*S*,6*S*)-1-Cinnamyl-6-isobutyl-4-(2-phenylethyl)-3-phenylpiperazine-2,5-dione (40) A yellow oil was obtained in 56% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.42-7.16 (m, 15H), 6.52 (d, *J* 16.0 Hz, 1H), 6.11-6.05 (m, 1H), 4.96 (s, 1H), 4.72-4.67 (m, 1H), 4.37-4.32 (m, 1H), 4.04-3.94 (m, 1H), 3.54-3.48 (m, 1H), 2.96-2.82 (m, 3H), 1.93-1.80 (m, 1H), 1.45-1.34 (m, 2H), 0.92 (d, *J* 6.4 Hz, 3H), 0.80 (d, *J* 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.3, 165.0, 138.1, 136.1, 135.3, 134.5, 128.9, 128.7, 128.6, 128.5, 128.4, 128.1, 126.7, 126.5, 126.1, 122.9, 64.2, 57.6, 47.8, 46.8, 42.8, 33.5, 25.0, 23.1, 21.6; HRMS calcd for $C_{31}H_{35}N_2O_2$ (M^++1): 467.2698. Found 467.2691.

(3*S*,6*S*)-1-Cinnamyl-4-(4-methoxybenzyl)-6-methyl-3-phenyl piperazine-2,5-dione (41) A yellow oil was obtained in 77% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.37-6.82 (m, 14H), 6.47 (d, *J* 16.0 Hz, 1H), 6.11-6.04 (m, 1H), 5.53 (d, *J* 14.8 Hz, 1H), 5.04 (s, 1H), 4.58-4.52 (m, 1H), 4.20 (q, *J* 7.2 Hz, 1H), 3.80 (s, 3H), 3.70-3.64 (m, 1H), 3.51 (d, *J* 14.8 Hz, 1H), 1.53 (d, *J* 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.8, 164.4, 159.5, 136.0, 135.1, 134.2, 130.1, 129.1, 128.6, 128.1, 126.7, 126.5, 122.7, 114.3, 114.2, 62.0, 55.5, 55.3, 47.0, 46.4, 19.4; HRMS: calcd. for $C_{28}H_{29}N_2O_3$ (M^++1) 441.2178; Found 441.2178.

(3*R*,8*aS*)-2-(2-Phenylethyl)-3-phenylhexahydropyrrolo[1,2-*a*]pyrazine -1,4-dione (42) A colorless oil was obtained in 66% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.39-7.15 (m, 10H), 5.00 (s, 1H), 4.33-4.26 (m, 1H), 4.01-3.97 (m, 1H), 3.63-3.56 (m, 1H), 3.42-3.37 (m, 1H), 3.03-2.84 (m, 3H), 2.38-2.32 (m, 1H), 2.05-1.92 (m, 2H), 1.80-1.78 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 168.1, 164.1, 138.0, 134.4, 129.2, 128.8, 128.6, 126.7, 125.7, 66.2, 58.2, 47.2, 45.7, 34.0, 29.2, 22.5; HRMS calcd for $C_{21}H_{23}N_2O_2$ (M^++1): 335.1760. Found 335.1762.

(3*R*,8*aS*)-2-(4-Methoxybenzyl)-3-phenylhexahydropyrrolo[1,2-*a*] pyrazine-1,4-dione (43) A colorless oil was obtained in 87% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.42-6.81 (m, 9H), 5.45 (d, *J* 14.4 Hz, 1H), 4.99 (s, 1H), 4.17-4.13 (m, 1H), 3.81 (s, 3H), 3.66-3.59 (m, 2H), 3.43-3.38 (m, 1H), 2.48-2.43 (m, 1H), 2.16-1.82 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 168.0, 163.9, 159.4,

134.2, 129.9, 129.3, 128.6, 127.5, 125.9, 114.3, 64.4, 58.3, 55.3, 47.3, 45.7, 29.5, 22.4; HRMS: calcd. for $C_{21}H_{23}N_2O_3$ (M^++1): 351.1709. Found 351.1709.

(3*R*,8*aS*)-2-(4-Methoxybenzyl)-3-methylhexahydropyrrolo[1,2-*a*] pyrazine-1,4-dione (44) A colorless oil was obtained in 76% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.19-7.13 (m, 2H), 6.86-6.83 (m, 2H), 5.30 (s, 1H), 4.93 (d, *J* 14.8 Hz, 1H), 4.17-4.11 (m, 2H), 3.92-3.87 (m, 1H), 3.79 (s, 3H), 3.63-3.51 (m, 2H), 2.48-2.44 (m, 1H), 2.11-1.81 (m, 3H), 1.35 (d, *J* 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.1, 166.9, 159.4, 129.8, 128.6, 114.3, 58.4, 57.5, 55.3, 47.1, 45.5, 29.4, 22.5, 16.7. The spectral data of **44** were identical to those of the authentic materials reported previously.[26]

General procedure for the preparation of diastereomeric mixtures of α-bromo tertiary amides. *N*-Alkyl-L-amino acid methyl ester (1.0 equiv), bromoacetic acid (1.0 equiv), DMAP (0.1 equiv) and DCC (1.1 equiv) were dissolved in CH_2Cl_2 and stirred at room temperature for 3 h. The mixture was then worked up by extraction with EtOAc and the organic phase was dried over $MgSO_4$. Filtration and concentration provided the crude product that was purified by column chromatography on silica gel. A 1:1 mixture of two diastereomers was obtained in 35-58% yields. No further attempts were made to optimize the yields. (Experimental procedures for the preparation of **1**, **12**, **13**, **14**, **15**, **32, 33** and **34** were described in previous publications.[14])

***N*-Benzyl-*N*-[α-bromo-α-(4-chlorophenyl)acetyl]-(*S*)-leucine methyl ester (16)** ^{1}H NMR ($CDCl_3$, 400 MHz, two rotamers of two diastereomers) 7.97-7.17 (m, 9H), 5.42, 5.37 (s, 1H), 5.15-4.45 (m, 3H), 3.72, 3.68, 3.56, 3.50 (s, 3H), 1.82 (m, 1H), 1.66-1.52 (m, 2H), 0.95-0.75 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.6, 168.7, 136.9, 136.7, 135.1, 134.4, 131.2, 130.7, 130.6, 129.2, 128.9, 128.7, 128.4, 128.1, 128.0, 126.1, 57.5, 56.4, 52.2, 52.1, 50.4, 49.4, 44.8, 44.2, 38.4, 38.2, 25.3, 25.1, 22.7, 22.4, 22.3; HRMS: calcd. for $C_{22}H_{26}BrClNO_3$ (M^++1) 466.0785; found 466.0785.

***N*-Benzyl-*N*-[α-bromo-α-(4-bromophenyl)acetyl]-(*S*)-leucine methyl ester (17)** ^{1}H NMR ($CDCl_3$, 400 MHz, two rotamers of two diastereomers) 7.47-7.19 (m, 9H), 5.44, 5.42 (s, 1H), 5.04-4.50 (m, 3H), 3.71, 3.67, 3.63, 3.58 (s, 3H), 1.90-1.82 (m, 1H), 1.58-1.51 (m, 2H), 0.94-0.76 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.5, 171.4, 168.6, 168.4, 136.9, 136.7, 136.5, 134.8, 134.6, 132.2, 131.9, 131.8, 131.7, 131.3, 131.0, 130.9, 130.3, 130.1, 129.8, 129.2, 128.9, 128.6, 128.4, 128.1, 128.0, 127.7, 127.2, 126.4, 126.3, 126.2, 126.1, 123.5, 123.4, 59.1, 57.5, 57.4, 56.8, 56.2, 52.2, 52.1, 51.7, 50.3, 49.6, 44.8, 44.3, 42.6, 38.4, 38.3, 38.2, 25.3, 25.2, 25.1, 24.9, 22.8, 22.7, 22.6, 22.4, 22.3, 22.2; HRMS: calcd. for $C_{22}H_{26}Br_2NO_3$ (M^++1) 510.0279; found 510.0279.

***N*-Benzyl-*N*-(α-bromopropionyl)-(*S*)-leucine methyl ester (18)** ^{1}H NMR ($CDCl_3$, 400 MHz, two rotamers of two diastereomers) 7.40-7.19 (m, 5H), 5.16-4.38 (m, 4H), 3.72-3.41 (s, 3H), 1.95-1.25 (m, 6H), 0.93-0.75 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, two rotamers of two diastereomers) 171.7, 171.5, 170.7, 170.6, 137.0, 136.6, 129.0, 128.9, 128.4, 127.8, 127.7, 127.3, 126.2, 126.1, 57.6, 55.4, 52.3, 51.9, 50.8, 48.8, 39.1, 39.0, 38.5, 37.9, 25.3, 24.9, 24.8, 22.9, 22.5, 22.3, 22.2, 21.4; HRMS: calcd. for $C_{17}H_{25}BrNO_3$ (M^++1) 370.1018; found 370.1010.

***N*-Benzyl-*N*-(α-bromobutanoyl)-(*S*)-leucine methyl ester (19)** ^{1}H NMR ($CDCl_3$, 400 MHz, two rotamers of two diastereomers) 7.40-7.22 (m, 5H), 5.13-4.08 (m, 4H), 3.72-3.49 (s, 3H), 2.25-0.68 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz, two rotamers of two diastereomers) 171.6, 170.0, 137.0, 136.7, 128.9, 128.8, 128.3, 127.8, 127.7, 126.2, 57.8, 55.6, 52.2, 51.9, 50.9, 49.0, 46.0, 45.6, 38.5, 37.9, 28.4, 28.3, 25.3, 24.9, 22.8, 22.5, 22.3, 22.2, 12.2; HRMS: calcd. for $C_{18}H_{27}BrNO_3$ (M^++1) 384.1174; found 384.1183.

***N*-(α-Bromo-α-phenylacetyl)-*N*-(4-methoxybenzyl)-(*S*)-leucine methyl ester (28)** ^{1}H NMR ($CDCl_3$, 400 MHz, two rotamers of two diastereomers) 7.41-6.89 (m, 9H), 5.56, 5.52 (s, 1H), 5.02-4.43 (m, 3H), 3.82, 3.64, 3.57 (s, 3H), 1.90-1.83 (m, 1H), 1.64-1.49 (m, 2H), 0.93-0.77 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.6, 168.7, 168.2, 159.3, 136.0, 135.9, 129.1, 129.0, 128.7, 128.6, 128.5, 128.4, 127.6, 127.5, 114.4, 113.7, 57.2, 56.7, 55.4, 52.1, 52.0, 49.3, 46.7, 46.2, 38.3, 38.2, 25.2, 25.1, 22.7, 22.5, 22.3; HRMS: calcd. for $C_{23}H_{29}BrNO_4$ (M^++1) 462.1280; found 462.1280.

***N*-(α-Bromo-α-phenylacetyl)-*N*-(4-methoxybenzyl)-(*S*)-alanine methyl ester (29)** ^{1}H NMR ($CDCl_3$, 400 MHz, two rotamers of two diastereomers) 7.46-6.89 (m, 9H), 5.62, 5.51, 5.27 (s, 1H), 4.74-4.46 (m, 3H), 3.81, 3.76, 3.69, 3.66 (s, 6H), 1.41, 1.37 (d, *J* 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, two rotamers of two diastereomers) 171.6, 168.3, 167.9, 159.3, 136.0, 129.2, 129.1, 128.7, 128.6, 128.5, 128.1, 127.6, 127.5, 114.5, 114.4, 55.4, 55.2, 55.1, 52.3, 50.3, 50.0, 47.8, 45.8, 14.5; HRMS: calcd. for $C_{20}H_{23}BrNO_4$ (M^++1) 420.0810; found 420.0799.

***N*-(α-Bromopropionyl)-*N*-(4-methoxybenzyl)-(*S*)-alanine methyl ester (30)** ^{1}H NMR ($CDCl_3$, 400 MHz, two rotamers of two diastereomers) 7.40-7.19 (m, 4H), 5.15-4.36 (m, 4H), 3.73, 3.58, 3.47 (s, 6H), 1.88, 1.77 (d, *J* 7.2 Hz, 3H), 0.93-0.74 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, two rotamers of two diastereomers) 171.7, 170.6, 137.0, 129.0, 128.9, 128.4, 127.8, 127.3, 126.1, 57.6, 52.3, 50.8, 39.0, 38.3, 37.9, 25.3, 22.9, 22.5, 22.3, 22.2, 21.4; HRMS: calcd. for $C_{15}H_{21}BrNO_4$ (M^++1) 358.0654; found 358.0654.

***N*-(α-Bromo-α-phenylacetyl)-*N*-cinnamyl-(*S*)-leucine methyl ester (31)** ^{1}H NMR ($CDCl_3$, 400 MHz, two rotamers of two diastereomers) 7.54-7.26 (m, 10H), 6.54 (m, 1H), 6.13 (m, 1H), 5.80, 5.78, 5.76 (s, 1H), 5.14, 4.98 (m, 1H), 4.32-4.00 (m, 2H), 3.68, 3.62 (s, 3H), 1.87-1.64 (m, 3H), 0.98-0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, two rotamers of two diastereomers) 171.8, 168.6, 168.4, 136.2, 136.0, 135.8, 132.5, 129.1, 128.8, 128.7, 128.4, 128.2, 126.5, 125.1, 56.7, 56.1, 52.3, 52.1, 48.7, 48.1, 46.5, 38.0, 25.1, 25.0, 23.0, 22.8, 22.1, 22.0; HRMS: calcd. for $C_{24}H_{29}BrNO_3$ (M^++1) 458.1331; found 458.1327.

Supplementary Material

The NMR of new compounds.

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References

1. Martins, M. B.; Carvalho, I. *Tetrahedron* **2007**, *63*, 9923. http://dx.doi.org/10.1016/j.tet.2007.04.105
2. Borthwick, A. D. *Chem. Rev.* **2012**, *112,* 3641. http://dx.doi.org/10.1021/cr200398y
3. Wang, H.; Usui, T.; Osada, H.; Ganesan, A. *J. Med. Chem.* **2000,** *43,* 1577. http://dx.doi.org/10.1021/jm9905662
4. Airaghi, F.; Fiorati, A.; Lesma, G.; Musolino, M.; Sacchetti, A.; Silvani, A. *Beilstein J. Org. Chem.* **2013**, *9,* 147. http://dx.doi.org/10.3762/bjoc.9.17
5. Panzeri, S.; Zanella, S.; Arosio, D.; Vahdati, L.; Corso, A. D.; Pignataro, L.; Paolillo, M.; Schinelli, S.; Belvisi, L.; Gennari, C.; Piarulli, U. *Chem. Eur. J.* **2015**, *21*, 6265. http://dx.doi.org/10.1002/chem.201406567
6. Zhang, H.; Wang, Q.; Ning, X.; Hang, H.; Ma, J.; Yang, X.; Lu, X.; Zhang, J.; Li, Y.; Niu, C.; Song, H.; Wang, X.; Wang, P. G. *J. Agric. Food Chem.* **2015**, *63*, 3734. http://dx.doi.org/10.1021/jf506153t
7. Bianco, A.; Sonksen, C. P.; Roepstorff, P.; Briand, J.-P. *J. Org. Chem.* **2000**, *65,* 2179. http://dx.doi.org/10.1021/jo991818+
8. Veerman, J. J. N.; Bon, R. S.; Hue, B. T. B.; Girones, D.; Rutjes, F. P. J. T.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2003**, *68*, 4486. http://dx.doi.org/10.1021/jo0342572
9. Tullberg, M.; Grøtli, M.; Luthman, K. *J. Org. Chem.* **2007**, *72*, 195. http://dx.doi.org/10.1021/jo0619635
10. Santra, S.; Andreana, P. R. *Org. Lett*. **2007**, *9*, 5035. http://dx.doi.org/10.1021/ol702256t
11. Nikulnikov, M.; Shumsky, A.; Krasavin, M. *Synthesis* **2015**, *15*, 2527.
12. Lim, H. J.; Gallucci, J. C.; RajanBabu, T. V. *Org. Lett*. **2010**, *12*, 2162. http://dx.doi.org/10.1021/ol100663y
13. Jida, M.; Tourwé, D.; Ballet, S. *RSC Adv.* **2014**, *4*, 38159. http://dx.doi.org/10.1039/C4RA05981F
14. Baek, J.; Kang, S. Y.; Im, C.; Park, Y. S. *Eur. J. Org. Chem.* **2014**, 2780. http://dx.doi.org/10.1002/ejoc.201301936

15. The enantiomeric purity of **2** was confirmed to be >99:1 er by chiral stationary phase HPLC (Chiralpak AD-H column) using racemic **2** as a standard.
16. The configurational stability of tetrasubstituted 2,5-diketopiperazine **2** under the reaction conditions was examined by the treatment of **2** (85:15 dr) with benzylamine, TBAI and DIEA in CH_3CN for two days. No epimerization was detected by ^{1}H-NMR, thus ruling out the possibility of epimerization after replacement of Br with the nucleophile.
17. Nam, J.; Chang, J.-y.; Shin, E.-k.; Kim, H. J.; Kim, Y.; Jang, S.; Park, Y. S. *Tetrahedron* **2004**, *60,* 6311. http://dx.doi.org/10.1016/j.tet.2004.05.094
18. Caddick, S.; Afonso, C. A. M.; Candeias, S. X.; Hitchcock, P. B.; Jenkins, K.; Murtagh, L.; Pardoe, D.; Santos A. G.; Treweeke, N. R.; Weaving, R. *Tetrahedron* **2001**, *57*, 6589. http://dx.doi.org/10.1016/S0040-4020(01)00550-6
19. Devine, P. N.; Foster, B. S.; Grabowski, E. J. J.; Reider, P. J. *Heterocycles* **2002**, *58*, 119. http://dx.doi.org/10.3987/COM-02-S(M)54
20. Valenrod, Y.; Myung, J.; Ben, R. N. *Tetrahedron Lett.* **2004**, *45,* 2545. http://dx.doi.org/10.1016/j.tetlet.2004.02.004
21. Bull, S. D.; Davies, S. G.; Garner, A. C.; O'Shea, M. D *J. Chem. Soc*., *Perkin Trans. 1* **2001**, 3281.
22. Bull, S. D.; Davies, S. G.; Garner, Savory, A. G.; Snow, E. D. E. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2004**, *15*, 3989. http://dx.doi.org/10.1016/j.tetasy.2004.11.022
23. The treatment of **38** with CAN to remove both *p*-methoxybenzyl groups afforded *cis*-5-methyl-3-phenyl-2,5-diketopiperazine.
24. Khimiuk, A. Y.; Korennykh, A. V.; van Langen, L. M.; van Rantwijk, F.; Sheldonb, R. A.; Svedas, V. K. *Tetrahedron: Asymmetry* **2003***, 14*, 3123. http://dx.doi.org/10.1016/j.tetasy.2003.08.011
25. The configuration of **39** and **44** was determined by comparing their NMR spectra with those of previously reported compounds.
26. Pichowicz, M.; Simpkins, N. S.; Blake, A. J.; Wilson, C. *Tetrahedron* **2008**, *64*, 3713. http://dx.doi.org/10.1016/j.tet.2008.02.020

