Unusual C=C Bond Migration in 3-Ylidene-2,5-piperazinediones

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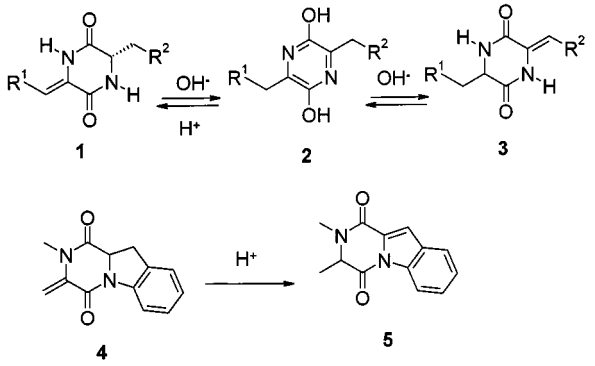
Treatment of 3-alkylidene or 3-benzylidene-2,5-piperazinediones **6** with catalytic amounts of acid gives rise to the formation of isomers **7** by migration of the C=C bond into the alkyl substituent at position 6, or results in mixtures of racemic **7** and *E* isomers **8**. The existence of tautomeric equilibria is discussed.

Introduction

3-Ylidene-2,5-piperazinediones (3-ylidene-2,5-diketopiperazines) **1** and **6** occur in nature, such as in plants or fungi, and can also be synthesized. They are cyclic dipeptides of a chiral amino acid and an achiral didehydroamino acid, and have generated wide interest as versatile building blocks for bicyclic *N*-heterocycles and amino acids.[1] In particular, additions to the C=C bond are of interest for the synthesis of natural and unnatural α-amino acid derivatives. Both nucleophiles and electrophiles may add in this way, exploiting the Michael acceptor and the enamine reactivity of the 3-ylidene-2,5-piperazinedione structure, respectively. In the case of the *N*,*N*′-unsubstituted 6-benzyl compound **1** (R^1 = H, R^2 = Ph), a migration under basic conditions of the C=C bond from position 3 to position 6, giving rise to the corresponding isomer **3**, was found by Bergmann et al. (Scheme 1).[2] This rearrangement was driven by the thermodynamic stability of the conjugated benzylidene system formed in **3** (R^2 = Ph). The transformation very likely involves the tautomeric 2,5-dihydroxypyrazines **2** (R^1 = H, R^2 = Ph). Such compounds **2** could be obtained by treating **1** with alkali at 100 °C, while rearrangement of **2** to **1** occurred under acid conditions.[3,4] A migration of the C=C bond was also reported for a bridged *N*,*N*′-disubstituted 3-methylene-2,5-piperazinedione **4**, giving the thermodynamically favoured aromatic indole **5**.[5] This reaction was catalysed by acids. No mechanism has been proposed. In our investigations of acid-catalysed addition reactions of π-electron-rich *N*-heterocycles to 3-ylidene-2,5-piperazinediones **6** we found that a C=C bond migration similar to the cases shown in Scheme 1 occurred, although compounds **6** are *N*,*N*′-disubstituted (R^3, $R^4 \neq$ H) and the conjugated π-system was not enlarged in this reaction.[6] This rearrangement parallels the transformation of **1** into **3** but cannot involve aromatic intermediates such as **2**. Moreover, acid conditions are necessary, rather than base catalysis. We report here details of this rearrangement of enantiopure *N*,*N*′-disubstituted, *N*-monosubstituted and *N*-unsubstituted 3-ylidene-2,5-piperazinediones **6** as well as that of the corresponding *E* isomers **8**.



Scheme 1. Known C=C bond migration

Results and Discussion

The rearrangements of 3-ylidene-2,5-diketopiperazinediones were performed in dioxane with catalytic amounts of 48% aqueous HBr (Scheme 2). The *N*,*N*′-disubstituted proline derivatives **6a−c** [$R^2/R^3 = (CH_2)_2$, R^4 = Me] completely rearranged to **7** when refluxed (Table 1, entries 1−3). Considering the known case where the *N*,*N*′-unsubstituted 6-benzyl-2,5-piperazinedione **1** (R^1 = H, R^2 = Ph) rearranged to the conjugated benzylidene product **3** under basic conditions,[2] the "deconjugation" occurring with the *N*,*N*′-disubstituted benzylidene derivative **6c** (R^1 = Ph) in the course of the acid-catalysed transformation into **7c** (entry 3) is peculiar. Under similar conditions the non-bridged *N*,*N*′-disubstituted **6d** gave an inseparable mixture of the rearranged product **7d** and the racemic *E* isomer **8d** (entry 4). At room temperature, only the optically active *E* isomer **8d** was obtained as a major product, together with unchanged starting material (entry 5). If a hydrogen atom was present at position 4 (R^4 = H), the tendency of 3-ylidene-2,5-piperazinediones **6** to rearrange to **7** diminished even if longer reaction times were applied. Low yields of **7** were isolated, together with racemised starting material (entries 6, 7). Since analogous treatment of the rearranged piperazinedione **7f** gave almost the same reaction mixture, i.e. ***rac*-6** and **7f** (80:20) as found for 3-ylidene-2,5-diketopiperazine **6f** (entries 7 and 8), the existence of an equilibrium is indicated. With regard to the mechanism of these reac-

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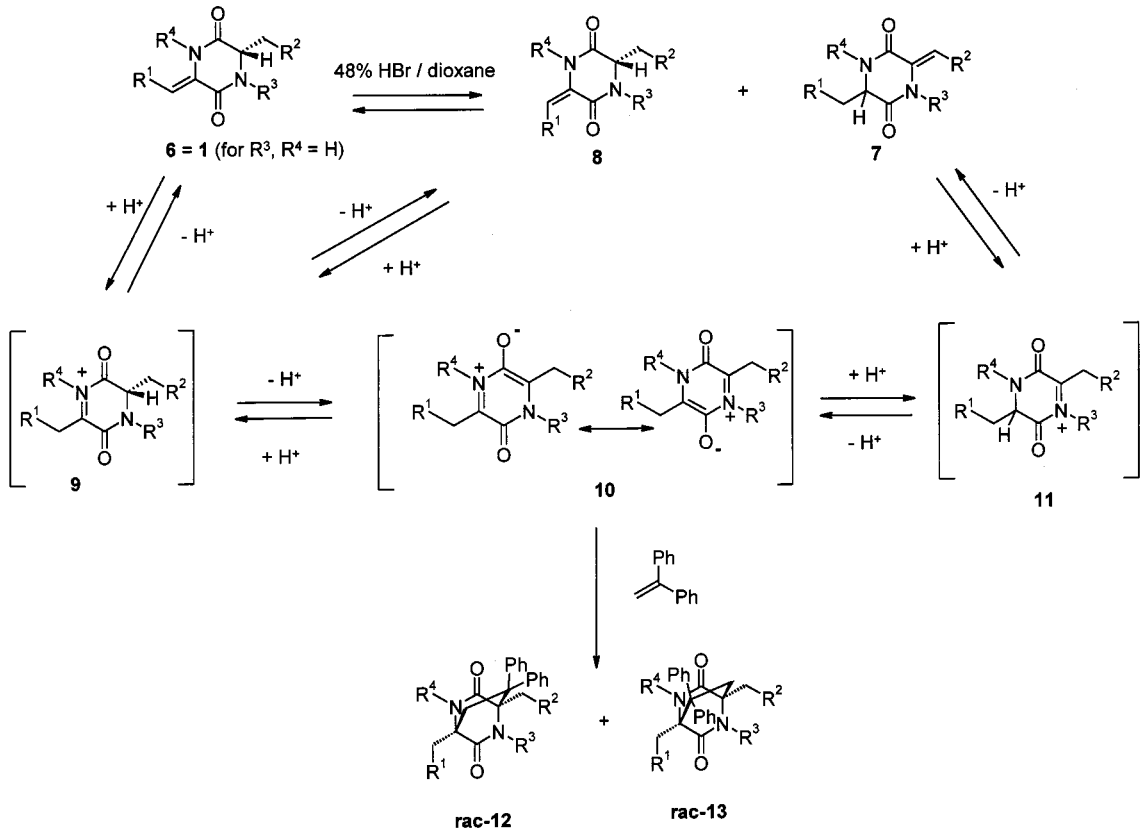


Scheme 2. Double bond migration, isomerisation and [4+2]-cycloaddition at (*Z*)-3-ylidene-2,5-piperazinediones

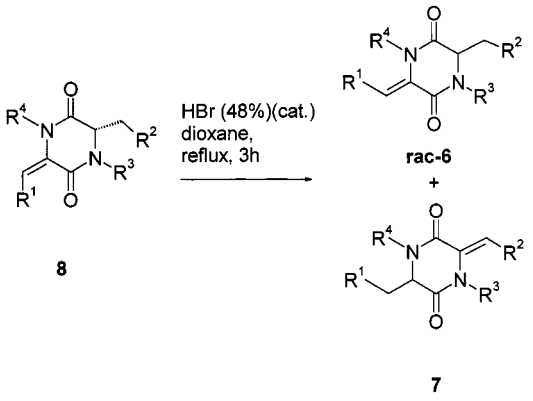
Table 1. Compounds **6**, ***rac*-6**, **7** and **8** obtained after acid treatment of 3-ylidene-2,5-piperazinediones **6**, **7** and **8**

Entry	Reactant	R^1	R^2, R^3	R^4	Reaction conditions	Reaction products (% isolated yield)				
						6	***rac*-6**	**7**	**8**	***rac*-8**
1	**6a**	H	$(CH_2)_2$	Me	reflux, 1 h			**a** (82)		
2	**6b**	*i*Pr	$(CH_2)_2$	Me	reflux, 45 min			**b** (81)		
3	**6c**	Ph	$(CH_2)_2$	Me	reflux, 1.5 h			**c** (93)		
4	**6d**	*i*Pr	H, Me	Me	reflux, 80 min			**d** (58)[a]		**d** (24)[a]
5					r. t., 15 h	**d** (20)[b]			**d** (55)[c]	
6	**6e**	*i*Pr	$(CH_2)_2$	H	reflux, 3 h		**e** (60)	**e** (39)		
7	**6f**	Ph	$(CH_2)_2$	H	reflux, 3 or 7 h		**f** (75)	**f** (25)		
8	**7f**	Ph	$(CH_2)_2$	H	reflux, 3h		**f** (80)[a]	**f** (20)[a]		
9	**8f**	Ph	$(CH_2)_2$	H	reflux, 3h		**f** (75)	**f** (23)		
10	**6g**	*i*Pr	H, H	H	reflux, 3h		**g** (95)[a] **g** (91)			**g** (5)[a]
11	**8g**	*i*Pr	H, H	H	reflux, 3h		**g** (95)[a] **g** (91)			**g** (5)[a]

[a] Determined by ^{1}H NMR and ^{13}C NMR. – [b] Optical rotation did not change during the reaction. – [c] *ee* = 97%, determined by chiral HPLC.

tions (vide infra), it is important that the corresponding *E* isomer **8f** gave the same products ***rac*-6f** and **7f** in the same ratio (entry 9 and Scheme 3). Refluxing the *N*,*N*′-unsubstituted 3-alkylidene-2,5-piperazinedione **6g** in dioxane/HBr led only to traces of the corresponding *E* isomer ***rac*-8g** while the starting material racemised (entry 10); i.e. no migration of the C=C bond occurred. Again, an equilibrium is likely since analogous treatment of the pure *E* isomer **8g** gave a mixture of ***rac*-6g** and ***rac*-8g** in the same ratio (entry 11 and Scheme 3). This type of *E*/*Z* isomerisation has been reported for a 3-benzylidene-2,5-piperazinedione under photochemical conditions.[4,7]

A suitable mechanism (see Scheme 2) involves protonation of 3-ylidene-2,5-piperazinediones **6**, affording the cyclic *N*-acyliminium salts **9**. Similar intermediates have been proposed before in acid-catalysed additions of nucleophiles to the endocyclic sp^2-carbon atom of the alkene functionality in 3-ylidene-2,5-diketopiperazines.[6,8–10] The *N*-acyliminium salts **9** could be deprotonated not only at the R^1CH_2 group, reverting to starting material **6** or affording



Scheme 3. Double bond migration and *E*/*Z* isomerisation at (*E*)-3-ylidene-2,5-piperazinediones

the *E* isomer **8**, but also at position 6 of the piperazine ring; i.e. at the R^2CH_2 group, giving rise to mesoionic piperazines **10**, which could be reprotonated at position 3 to give *N*-acyliminium salts **11**. Final deprotonation of the R^2CH_2 group would afford **7**, leaving the C=C bond shifted with respect to compounds **6**. The formation of the *E* isomers **8** and the optically inactive ***rac*-6** on acid treatment of the 3-ylidene-2,5-piperazinediones **6** could be explained by a non-stereoselective deprotonation of the *N*-acyliminium salts **9** at the R^1CH_2 group. Presumably, the transformation of **9** into **10** needs a higher activation than the isomerisation to **8** as indicated by the temperature effect (see entry 5). Evidence for intermediate mesoionic piperazines **10** was found in the formation of the [4+2] cycloadducts ***rac*-12** and ***rac*-13** in the reaction of **6e** with 1,1-diphenylethene.[11] The isomerisation of the *E* isomers **8** can be explained in the same way as for the *Z* isomers: i.e. by the formation of cyclic *N*-acyliminium salts **9**, which are transformed to racemic **6** or **7f** according to Scheme 2.

Despite the mechanism of the transformation of **6** into **7** and **8**, the question of the driving force of these processes has to be considered. It could be assumed that these processes are thermodynamically driven by the relative stability of the tautomers **6** and **7** i.e. tautomers **6** or **7** should be more stable with the C=C bond in the side chain along with the less bulky substituent R^1 or R^2, respectively, where the steric repulsion between R^1 and R^4 is lower than between R^2 and R^3 or vice versa. As far as proline derivatives **6** and **7** ($R^2/R^3 = CH_2CH_2$) are concerned, rearrangement from **6** to **7** does not greatly increase the steric repulsion of R^2 and R^3 because of the fixed, bridging position of both substituents in both tautomeric forms due to bridging. Therefore, the release in steric repulsion of substituents R^1 and R^4 becomes the determining factor, even overriding the loss of conjugation found in the rearrangement of the 3-benzylidene-2-methyl-2,5-piperazinedione **(6c)** into **7c** (entry 3). If the steric repulsion is reduced by putting a hydrogen atom (R^4 = H) rather than a methyl group (R^4 = Me) at position 2 of proline-derived 3-ylidene-2,5-piperazinediones such as in compounds **6e** and **6f**, the release in steric repulsion during transformation into **7** is lower and thus the equilibrium is more toward **6** (see entry 6, 7 and 8). The relative thermodynamic stability of isomers **6** and **7** was also investigated by quantum chemical calculations on compounds **6a** and 7**a,** and **6c** and **7c**. Calculations performed at a semiempirical level (AM1, PM3) were found to be unsuitable for solving the problem. Only the use of DFT methods and high basis sets provided satisfactory results (see Table 2). Thus, **7a** was found to be more stable than **6a** by about 2 kcal/mol at B3PW91/6−31G*//HF/3−21G level (including zero point energy). It should be noted that an ab initio method at low level (HF/3−21G) predicted the opposite, i.e. that **6a** would be more stable than **7a**. Furthermore, the zero point energy amounts to a considerable portion of the 2 kcal/mol (0.7 kcal/mol) mentioned above.

While the higher stability of **7a** is reasonable, we were surprised about the exclusive formation of **7c**, which occurs with a loss of conjugation. This result could not be confirmed using the calculation method that had been successful in the case of **6a/7a**. We found that **6c** is more stable than **7c** by 1 kcal/mol at the B3PW91/6−31G*//HF/3−21G level. While the zero point energy has the correct sign compared with the experimental findings, the pure electronic energy is responsible for the incorrect result. Upon addition of diffuse functions to the basis set (6−31+G*), the energy difference between **6c** and **7c** is lowered to 0.3 kcal/mol and the utilisation of a more flexible basis set (6−311++G**) brings this difference to ± 0 kcal/mol. Obviously, the correct quantum chemical description of the reaction **6** → 7 requires a very high level of theory and the consideration of the zero point energy is of great importance. This indicates that molecular flexibility and steric effects play an important role in this reaction.

Conclusion

In summary, a novel, acid-catalysed tautomerism of 3-ylidene-2,5-piperazinediones **6**, **7** and **8** by migration of the C=C bond was found. The reaction is likely to proceed via intermediate *N*-acyliminium salts and mesoionic piperazines and be driven by entropic effects of the tautomers. In addition, acid-catalysed *E*/*Z*-isomerisation was observed.

Experimental Section

General Remarks: ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively, with a Bruker AC-300 with TMS as internal standard. Optical rotation was determined with a Perkin−Elmer polarimeter 241. Mass spectra (HP 5995 A) and high-resolution mass spectra (MAT 711, Varian) were measured at 70 eV. Some of the highly polar products did not give satisfactory microanalyses but showed clear NMR spectra and satisfactory high resolution mass spectra. Silica gel (0.04−0.063 mm, Merck) was used for preparative column chromatography. If not otherwise mentioned, chemicals were purchased from Aldrich or Merck.

Starting Materials: Starting materials were commercially available or were prepared according to the literature: (*S*)-2-methyl-3-methylenehexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**6a**),[13] (*S*)-2-methyl-3-[(*Z*)-benzylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-

Table 2. Ab initio and DFT calculations on compounds **6a**, **7a**, **6c** and **7c** [12]

entry	ZPE [kcal/mol][a]	B3PW91/6-31G* [a.u.]	B3PW91/6-31+G* [a.u.]	B3PW91/6-311++G** [a.u.]
6a	140.32	−609.91902	–	–
7a	139.66	−609.92117	–	–
6c	195.39	−840.88108	−840.90334	−841.09204
7c	194.98	−840.87877	−840.90230	−841.09139

[a] HF/3−21G.

dione (**6c**),[14] (*S*)-3-[(*Z*)-isobutylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**6e**),[14] (*S*)-3-[(*Z*)-benzylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**6f**).[14] The values for the optical rotation obtained were the same as those reported.

(*S*)-2-Methyl-3-[(*Z*)-isobutylidene]-hexahydro-pyrrolo[1,2-*a*]pyrazine-1,4-dione (6b): Sodium hydride (0.25 g, 95%, 10.0 mmol) was slowly added to a solution of **6e** (2.08 g, 10.0 mmol) in dry DMF (50 mL) with vigorous stirring under argon at room temperature. After stirring for an additional 10 minutes, methyl iodide (1.5 mL) was added. Two hours later, the mixture was evaporated under vacuum. The residue was mixed with saturated aqueous NaCl (75 mL) and extracted with $CHCl_3$ (3 × 50 mL). The organic phase was dried with Na_2SO_4 and evaporated under vacuum. The remaining material was separated by chromatographic column (acetone/$CHCl_3$/hexane, 1:2:3) to afford **6b** (1.39 g, 63%, R_f = 0.45) and starting material **6e** (0.04 g, 8%, R_f = 0.22). Compound **6b** could be obtained as colourless needles by recrystallisation from EtOAc/hexane. − M.p. 124−126 °C. − $[\alpha]_D^{20}$ = +197 (*c* = 1.1, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 1.01 (d, *J* = 6.5 Hz, 3 H, *Me*$_2$CHCH=C), 1.14 (d, *J* = 6.5 Hz, 3 H, *Me*$_2$CHCH=C), 1.90−2.13 (m, 3 H, CHC*H*$_2$C*H*$_2$CH$_2$N), 2.33 (m, 1 H, CHC*H*$_2$CH$_2$CH$_2$N), 2.72 (m, 1 H, Me$_2$C*H*CH=C), 3.22 (s, 3 H, CH_3N), 3.55 (m, 2 H, CH CH$_2$CH$_2$C*H*$_2$N), 4.04 (pseudo-t, 1 H, C*H*CH$_2$CH$_2$CH$_2$N), 5.92 (d, *J* = 10.8 Hz, 1 H, Me$_2$CHC*H*=C). − ^{13}C NMR ($CDCl_3$): δ = 22.7 (*Me*$_2$CHCH=C), 23.1 (CHCH$_2$*C*H$_2$CH$_2$N), 23.3 (*Me*$_2$CHCH=C), 27.4 (Me$_2$*C*HCH=C), 28.3 (CH*C*H$_2$CH$_2$CH$_2$N), 35.3 (*C*H$_3$N), 45.4 (CHCH$_2$CH$_2$*C*H$_2$N), 59.0 (*C*HCH$_2$CH$_2$CH$_2$N), 132.1 (Me$_2$CH*C*H=C), 132.9 (Me$_2$CHCH=*C*), 162.0 (C=O), 168.0 (C=O). − MS: *m*/*z* (%) = 223 (4) [M^+ + 1], 222 (24) [M^+], 208 (18), 179 (20), 165 (17), 92 (25), 82 (89), 70 (89), 41 (100). − $C_{12}H_{18}N_2O_2$ (222.3): calcd. C 64.84, H 8.16, N 12.60; found C 64.72, H 8.20, N 12.54.

(6*S*)-3-[(*Z*)-Isobutylidene]-6-methyl-2,5-piperazinedione (6g) and (6*S*)-3-[(*E*)-2-Isobutylidene]-6-methyl-2,5-piperazinedione (8g): *a) Introduction of the isobutylidene group*: A solution of (*S*)-3-methyl-2,5-piperazinedione (1.90 g, 14.8 mmol)[15,16] in acetic anhydride acetic acid (20 mL) was heated at 130 °C under argon for 7 h. After evaporation under argon the residue was mixed with saturated aqueous $NaHCO_3$ (50 mL) and extracted with $CHCl_3$ (3×50 mL). The organic phase was dried with Na_2SO_4 and evaporated under vacuum at 50 °C to give 3.30 g of crude (*S*)-1,4-diacetyl-3-methyl-2,5-piperazinedione (R_f = 0.6, EtOAc /hexane, 1:1). A solution of potassium *tert*-butoxide (1.714 g, 1 equiv.) in *tert*-butyl alcohol (24 mL) was added to a mixture of this crude piperazinedione (3.30 g), dry DMF (40 mL) and isobutyraldehyde (8.80 g, 8 equiv.) at 0 °C under argon. After stirring at room temp. for 6 h, the reaction mixture was acidified with acetic acid (3.5 mL), poured into water (100 mL) and extracted with EtOAc (4×50 mL). The organic phase was dried with Na_2SO_4 and evaporated under vacuum. The mixture of isomers was separated by column chromatography (EtOAc/hexane, 1:2), affording 2.26 g (68%) (*S*)-1-acetyl-3-[(*Z*)-isobutylidene]-6-methyl-2,5-piperazinedione and 0.78 g (24%) (*S*)-1-acetyl-3-[(*E*)-isobutylidene]-6-methyl-2,5-piperazinedione.

(*S*)-1-Acetyl-3-[(*Z*)-isobutylidene]-6-methyl-2,5-piperazinedione: Colourless crystals. − M.p. 95−98 °C. − R_f = 0.45. − $[\alpha]_D^{20}$ = +39.0 (*c* = 1, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 1.02 and 1.04 (2d, *J* = 5.2 Hz, 6 H, *Me*$_2$CHCH=C), 1.39 (d, *J* = 7.1 Hz, 3 H, *Me*CH), 2.47 (s, 3 H, CH_3CO), 2.77 (m, 1 H, Me$_2$C*H*CH=C), 4.94 (q, *J* = 7.1 Hz, 1 H, MeC*H*), 6.11 (d, *J* = 10.4 Hz, 1 H, Me$_2$CHC*H*=C), 9.90 (s, 1 H, HN). − ^{13}C NMR ($CDCl_3$): δ = 18.0 (*Me*CH), 20.6 (*Me*$_2$CHCH=C), 24.4 (Me$_2$*C*HCH=C), 25.4 (*C*H$_3$CO), 51.0 (Me*C*H), 123.3 (Me$_2$CHCH=*C*), 131.0 (Me$_2$CH*C*H=C), 159.6 (C=O), 167.6 (C=O), 170.7 (C=O).

(*S*)-1-Acetyl-3-[(*E*)-isobutylidene]-6-methyl-2,5-piperazinedione: Colourless syrup. − R_f = 0.36. − ^{1}H NMR ($CDCl_3$): δ = 0.97 and 1.03 (2d, *J* = 6.6 Hz, 6 H, *Me*$_2$CHCH=C), 1.40 (d, *J* = 7.1 Hz, 3 H, *Me*CH), 2.47 (s, 3 H, CH_3CO), 3.48 (m, 1 H, Me$_2$C*H*CH=C), 4.94(q, *J* = 7.1 Hz, 1 H, MeC*H*), 5.58 (d, *J* = 9.9 Hz, 1 H, Me$_2$CHC*H*=C), 9.97 (s, 1 H, HN). ^{13}C NMR($CDCl_3$): δ = 19.2 (*Me*CH), 22.7 and 23.2 (*Me*$_2$CHCH=C), 27.1 (Me$_2$*C*HCH=C), 27.3 (*C*H$_3$CO), 52.6 (Me*C*H), 124.1 (Me$_2$CHCH=*C*), 139.0 (Me$_2$CH*C*H=C), 161.2 (C=O), 170.0 (C=O), 172.3 (C=O).

b) Deacetylation: Hydrazine hydrate (1.77 g, 35.4 mmol) was added to a solution of (*S*)-1-acetyl-3-[(*Z*)-isobutylidene]-6-methyl-2,5-piperazinedione (1.99 g, 8.9 mmol) in DMF (25 mL) at room temp. The suspension was stirred for 3 h and mixed with some ice (≈50 mL). The colourless product was filtered off and washed first with water and then with acetone. (*S*)-3-[(*Z*)-isobutylidene]-6-methyl-2,5-piperazinedione **6g**: Yield 1.46 g (90%). − Colourless needles. − M.p. 265 °C (dec.). − $[\alpha]_D^{20}$ = −10.8, $[\alpha]_{546}^{20}$ = −12.6 (*c* = 1, AcOH). ^{1}H NMR ($CDCl_3$/CF_3COOD, 6:1): δ = 1.12 and 1.14 (2d, *J* = 2.0 Hz, 6 H, *Me*$_2$CHCH=C), 1.64 (d, *J* = 7.0 Hz, 3 H, *Me*CH), 2.71 (m, 1 H, Me$_2$C*H*CH=C), 4.43 (q, *J* = 7.0 Hz, 1 H, MeC*H*), 6.24 (d, *J* = 10.5 Hz, 1 H, Me$_2$CHC*H*=C), 8.38 and 9.59 (2 bro.s, 2HN). − ^{13}C NMR ($CDCl_3$/CF_3COOD, 6:1): δ = 20.0 (*Me*CH), 21.4 and 21.5 (*Me*$_2$CHCH=C), 25.7 (Me$_2$*C*HCH=C), 51.3 (Me*C*H), 121.5 (Me$_2$CHCH=*C*), 134.0 (Me$_2$CH*C*H=C), 162.4 (C=O), 169.5 (C=O). − $C_9H_{14}N_2O_2$ (182.22): calcd. C 59.32, H 7.74, N 15.37; found C 59.21, H 7.80, N 15.30.

Analogous treatment of (*S*)-1-acetyl-3[(*E*)-isobutylidene]-6-methyl-2,5-piperazinedione (648 mg, 2.89 mmol) with hydrazine hydrate (578 mg, 11.56 mmol) in DMF (8 mL) afforded (*S*)-1-acetyl-3-[(*E*)-isobutylidene]-6-methyl-2,5-piperazinedione **8g**: Yield 456 mg (86%). − Colourless needles. − M.p. ≈260 °C (dec.). − $[\alpha]_D^{20}$ = +5.9, $[\alpha]_{546}^{20}$ = +7.4 (*c* = 1, AcOH). − ^{1}H NMR ($CDCl_3$: CF_3COOD, 6:1): δ = 0.92 (d, *J* = 6.7 Hz, 6 H, *Me*$_2$CHCH=C), 1.45 (d, *J* = 7.0 Hz, 3 H, *Me*CH), 3.51 (m, 1 H, Me$_2$C*H*CH=C), 4.22 (q, *J* = 7.0 Hz, 1 H, MeC*H*), 5.53 (d, *J* = 10.2 Hz, 1 H, Me$_2$CHC*H*=C), 8.04 and 9.38 (2 br.s, 2HN). − ^{13}C NMR ($CDCl_3$/CF_3COOD, 6:1): δ = 19.7 (*Me*CH), 22.0 and 22.1 (*Me*$_2$CHCH=C), 26.6 (Me$_2$*C*HCH=C), 51.0 (Me*C*H), 120.6 (Me$_2$CHCH=*C*),

140.3 ($Me_2CHCH=C$), 162.4 (C=O), 169.7 (C=O). − $C_9H_{14}N_2O_2$ (182.22): calcd. C 59.32, H 7.74, N 15.37; found C 59.29, H 7.81, N 15.34.

(*S*)-1,4,6-Trimethyl-3-[(*Z*)-isobutylidene]-2,5-piperazinedione (6d): Sodium hydride (95%, 342 mg, 13.52 mol) was slowly added to a solution of **6g** (1.23 g, 6.7 mmol) in dry DMF (60 mL) with vigorous stirring under argon at room temp. After stirring for an additional 0.5 h, methyl iodide (5 mL, 0.08 mol) was added. Stirring was continued for 45 min. The solvent was evaporated under vacuum at 40 °C. The residue was mixed with water (≈ 80 mL) and extracted with $CHCl_3$ (3 × 50 mL). The organic phase was dried with Na_2SO_4 and the solvent was evaporated to afford the target product **6d**, which was purified by column chromatography (EtOAc/hexane, 9:1), yield 1.33 g (93%). Colourless oil. − R_f = 0.37. − $[\alpha]_D^{20}$ = −138.9, $[\alpha]_{546}^{20}$ = −171.0 (*c* = 1, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 1.14 and 1.27 (2 d, *J* = 6.6 Hz, 6 H, Me_2CHCH=C), 1.50 (d, *J* = 7.0 Hz, 3 H, *Me*CH), 2.88 (m, 1 H, Me_2CHCH=C), 3.10 (s, 3 H, CH_3−N), 3.36 (s, 3 H, CH_3−N), 4.03 (q, *J* = 7.0 Hz, 1 H, MeC*H*), 6.12 (d, *J* = 10.8 Hz, 1 H, Me_2CHCH=C). − ^{13}C NMR ($CDCl_3$): δ = 17.2 (*Me*CH), 22.8 and 23.1(Me_2CHCH=C), 27.4 (Me_2CHCH=C), 32.4 and 35.3 (2 MeN), 59.5 (Me*C*H), 130.7 (Me_2CHCH=*C*), 132.6 (Me_2CHCH=C), 162.9 (C=O), 168.3 (C=O). − $C_{11}H_{18}N_2O_2$ (210.3): calcd. C 62.83, H 8.63, N 13.32; found C 62.71, H 8.71, N 13.39.

(*S*)-3-[(*E*)-Benzylidene]-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (8f): A solution of **6f** (1.323 g, 5.50 mmol) in dry MeOH (140 mL) was irradiated at room temperature under argon in a quartz reactor with a 125 W medium-pressure mercury lamp for 3 h. The mixture was evaporated under vacuum and then dissolved in CH_2Cl_2 (50 mL), mixed with silica gel (4 g) and evaporated under vacuum again. A chromatographic column loaded with silica gel was charged with the adsorbed sample and eluted with acetone/$CHCl_3$ (1:4). After evaporation of the solvent, 418 mg (18%) of the product **8f** (R_f = 0.33; starting material R_f = 0.48) were obtained. M.p. 170−175 °C (EtOAc/hexane). − $[\alpha]_{RT}^{D}$ = +48.7, $[\alpha]_{RT}^{546}$ = +61.5, (*c* = 1, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 1.84 (m, 1 H, $CH_2CH_2CH_2CH$), 1.96 (m, 2 H, $CH_2CH_2CH_2CH$), 2.32 (m, 1 H, $CH_2CH_2CH_2CH$), 3.49 (m, 1 H, $CH_2CH_2CH_2CH$), 3.61 (m, 1 H, $CH_2CH_2CH_2CH$), 4.15 (dd, J_1 = 6.9 Hz, J_2 = 9.2 Hz, 1 H, $CH_2CH_2CH_2CH$), 6.33 (s, 1 H, PhC*H*), 7.18 (m, 3 H, Ph), 7.45 (m, 2 H, Ph), 9.41 (s, 1 H, N*H*). − ^{13}C NMR ($CDCl_3$): δ = 22.1 ($CH_2CH_2CH_2CH$), 28.9 ($CH_2CH_2CH_2CH$), 45.7 ($CH_2CH_2CH_2CH$), 59.0 ($CH_2CH_2CH_2CH$), 122.6 (Ph*C*H), 127.2(PhCH=*C*), 127.8 (2 × CH_{Ph}), 128.0 (CH_{Ph}), 130.0 (2×CH_{Ph}), 133.6 (C_{Ph}), 157.9 (C=O), 168.1 (C=O). − $C_{14}H_{14}N_2O_2$ (242.3): calcd. C 69.41, H 5.82, N 11.56; found 69.43, H 5.88, N 11.43.

General Procedure for the Acid-Catalysed Isomerisation of 3-Ylidene-2,5-piperazinediones 6, 7 and 8: A solution of 3-ylidene-2,5-diketopiperazine **6, 7f**, **8f** or **8g** (0.5 mmol) in dioxane (8 mL) was refluxed or stirred at room temp. (see Table 1) under argon in the presence of aqueous HBr (48%, 1 drop). The solvent was removed under vacuum and the residue separated by column chromatography.

(3*R*/*S*)-3-Methyl-6-[(*Z*)-2-methylpropylidene]-2,5-piperazinedione (6g): Starting material **6g** (**8g** gave the same result), reflux 3 h. After evaporation of the solvent a sparingly soluble mixture of mainly racemic **6g** and racemic **8g** (95:5 according to ^{1}H NMR in $CDCl_3$/CF_3COOD, 2:1) was obtained. The major product **6g** could be separated in a pure form by addition of 2.5 g silica to the reaction mixture before evaporating the solvent. The remaining solid mixture was transferred onto a column with some hexane and was eluted with EtOAc/hexane (9:1). **6g:** Yield 91%. − R_f = 0.28 (**8g**: R_f = 0.49) − $[\alpha]_D^{20}$ = −4.8 (*c* = 2, AcOH). − For spectroscopic data see above.

2,3-Dimethyl-2,3,6,7-tetrahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (7a): Starting material **6a** (R_f = 0.55), reflux 1 h. − Yield 82%, colourless syrup. − R_f = 0.38 (acetone/$CHCl_3$, 1:2). − ^{1}H NMR ($CDCl_3$): δ = 1.48 (d, *J* = 7.0 Hz, 3 H, CH_3CH), 2.71 (m, 2 H, $CHCH_2CH_2N$), 2.95 (s, 3 H, CH_3N), 3.84−4.03 (m, 3 H, $CHCH_2CH_2N$ and CH_3CH), 6.07 (t, *J* = 3.0 Hz, 1 H, $CHCH_2CH_2N$). − ^{13}C NMR ($CDCl_3$): δ = 19.7 (CH_3CH), 28.2 ($CHCH_2CH_2N$), 32.0 (CH_3N), 45.9 ($CHCH_2CH_2N$), 60.3 (CH_3CH), 118.8 ($CHCH_2CH_2N$), 133.3 (C), 156.3 (C=O), 163.5 (C=O). − MS: *m*/*z* (%) = 181 (5.3) [M^+ + 1], 180 (44.3) [M^+], 165 (16.0), 137 (100). − HRMS ($C_9H_{12}N_2O_2$): calcd. 180.0899; found 180.0898.

3-Isobutyl-2,3,6,7-tetrahydro-2-methylpyrrolo[1,2-*a*]pyrazine-1,4-dione (7b): Starting material **6b** (R_f = 0.60), reflux 45 min. − Yield 81%, colourless syrup. − R_f = 0.42 (acetone/$CHCl_3$, 1:4), − ^{1}H NMR ($CDCl_3$): δ = 0.84 (t, *J* = 6.2, 6 H, Me_2CHCH_2CH), 1.67 (m, 1 H, Me_2CHCH_2CH), 1.77 (m, 2 H, Me_2CHCH_2CH), 2.71 (m, 2 H, $CHCH_2CH_2N$), 2.93 (s,3 H,CH_3N), 3.87−3.99 (m, 3 H, $CHCH_2CH_2N$ and Me_2CHCH_2CH), 6.08 (t, *J* = 3.0 Hz, 1 H, $CHCH_2CH_2N$). − ^{13}C NMR ($CDCl_3$): δ = 22.0 and 23.3 (Me_2CHCH_2CH), 24.0 (Me_2CHCH_2CH), 27.7 ($CHCH_2CH_2N$), 31.9 (CH_3N), 40.9 (Me_2CHCH_2CH), 45.3 ($CHCH_2CH_2N$), 62.9 (Me_2CHCH_2CH), 118.3 ($CHCH_2CH_2N$), 132.9 (C), 156.4 (C=O), 162.7 (C=O). − MS: *m*/*z* (%) = 223 (0.9) [M^+ + 1], 222 (5.1) [M^+], 179 (1.4), 167 (9.5), 166 (100), 137 (57.3). − HRMS ($C_{12}H_{18}N_2O_2$): calcd. 222.1368; found 222.1368.

3-Benzyl-2,3,6,7-tetrahydro-2-methylpyrrolo[1,2-*a*]pyrazine-1,4-dione (7c): Starting material **6c** (R_f = 0.64), reflux 1.5 h. − Yield 93%. − Amorphous colourless solid. − M.p.115−120 °C. −R_f = 0.33 (acetone/$CHCl_3$,1:4). − ^{1}H NMR ($CDCl_3$): δ = 2.33 (br. m, 2 H, $CHCH_2CH_2N$), 3.02 (s, 3 H,CH_3N), 3.06 (dd, J_1 = 4.2 and J_2 = 13.8 Hz, 1 H, *A*BX, PhCH_2CH), 3.18 (dd, J_1 = 3.4 and J_2 = 13.8 Hz, 1 H, A*B*X, PhCH_2CH), 3.66 (m, 2 H, $CHCH_2CH_2N$), 4.22 (dd, J_1 = 3.4 and J_2 = 4.2 Hz, 1 H, AB*X*, PhCH_2C*H*), 5.60 (t, *J* = 3.0 Hz, 1 H, $CHCH_2CH_2N$), 6.93 and 7.14 (2m, 5 H, Ph). − ^{13}C NMR($CDCl_3$): δ = 27.4 ($CHCH_2CH_2N$), 32.0 (CH_3N), 37.1 (PhCH_2CH), 44.7 ($CHCH_2CH_2N$), 65.0 (PhCH_2CH), 117.5 ($CHCH_2CH_2N$), 127.3 (CH_{Ph}), 128.2 and 129.4 (4CH_{Ph}), 132.2 (C), 133.9 (C_{Ph}), 156.6 (C=O), 161.7 (C=O). − MS: *m*/*z* (%) = 258 (0.2) [M^+ + 2], 257 (2.0) [M^+ + 1], 256 (10.5) [M^+], 166 (9.8), 165 (100) [M^+ − $PhCH_2$], 137 (11.5). − HRMS ($C_{15}H_{16}N_2O_2$) calcd. 256.1212; found 256.1214.

3-[(*E*)-isobutylidene]-(*S*)-1,4,6-Trimethyl-2,5-piperazinedione (8d): Starting material **6d** (R_f = 0.37), room temp. 15 h. − Yield 55%, 20% of **6d** recovered. − Colourless oil. − R_f = 0.55 (EtOAc /hexane, 9:1). $[\alpha]_D^{20}$ = −148.9, $[\alpha]_{546}^{20}$ = −183.1 (*c* = 2.2, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.94 and 1.06 (2d, *J* = 6.6, 6 H, Me_2CHCH=C), 1.35 (d, *J* = 7.0 Hz, 3 H, *Me*CH), 2.93 (s, 3 H, CH_3-N), 3.08 (s, 3 H, CH_3−N), 3.56 (m, 1 H, Me_2CHCH=C), 3.86 (q, *J* = 7.0 Hz, 1 H, MeC*H*), 5.30 (d, *J* = 9.8, 1 H, Me_2CHCH=C). − ^{13}C NMR ($CDCl_3$): δ = 17.9 (*Me*CH), 23.1 and 23.5 (Me_2CHCH=C), 26.5 (Me_2CHCH=C), 30.9 and 31.9 (NMe_2), 58.7 (Me*C*H), 128.7 (Me_2CHCH=*C*), 133.6 (Me_2CHCH=C), 160.2 (C=O), 166.9 (C=O). − MS: *m*/*z* (%) = 212 (0.6) [M^+ +2], 211 (5.2) [M^+ + 1], 210 (35.0) [M^+], 209 (2.4), 195 (26.8), 171 (13.6), 167 (37.6), 124 (13.4), 110 (14.0), 96 (39.2), 83 (10.5), 82 (77.2), 69 (28.1), 58 (57.4), 57 (27.4), 56 (52.3), 55 (31.6), 43 (33.3), 42 (100), 41 (45.0). − HRMS ($C_{11}H_{18}N_2O_2$): calcd. 210.1368; found 210.1370.

6-Isobutyl-1,4-dimethyl-3-methylene-2,5-piperazinedione (7d) and 6-[(*E*)-Isobutylidene]-1,3,4-trimethyl-2,5-piperazinedione 8d: Starting material **6d** (R_f = 0.37), reflux 80 min. A mixture of ***rac*-7d** and ***rac*-8d** was obtained as an inseparable mixture (R_f = 0.55, EtOAc/hexane, 9:1) (***rac*-7d**/***rac*-8d** = 70:30 according to ^{1}H NMR spectroscopy) in a total yield of 81%. NMR spectra were obtained from the mixture of ***rac*-7d** and ***rac*-8d**. ***rac*-7d:** ^{1}H NMR ($CDCl_3$): δ = 0.85 (d, J = 5.2, 6 H, Me_2CHCH$_2$CH), 1.64 (m, 3 H, Me$_2$C*H*CH$_2$CH), 2.96 (s, 3 H, CH$_3$−N), 3.13 (s, 3 H, CH$_3$−N), 3.95 (m, 1 H, Me$_2$CHCH$_2$C*H*), 4.85 (d, J = 0.9 Hz, 1 H, CH$_2$= C), 5.73 (d, J = 0.9 Hz, 1 H, CH$_2$=C). − ^{13}C NMR ($CDCl_3$): δ = 22.0 and 23.1 (Me_2CHCH$_2$CH), 24.2 (Me$_2$*C*HCH$_2$CH), 29.9 and 32.9 (2 MeN), 42.1 (Me$_2$CH*C*H$_2$CH), 61.3 (Me$_2$CHCH$_2$*C*H), 102.7 (*C*H$_2$=C), 137.4 (CH$_2$=*C*), 158.8 (C=O), 165.3 (C=O). For spectroscopic data of ***rac*-8d** see above.

2,3,6,7-Tetrahydro-3-isobutylpyrrolo[1,2-*a*]pyrazine-1,4-dione (7e): Starting material **6e** (R_f = 0.59), 3 h of reflux afforded 39% of **7e** and 60% of racemic ***rac*-6e**. − **7e:** Colourless needles. − M.p. 130−135 °C (EtOAc). − R_f = 0.40(acetone/$CHCl_3$, 1:2). − ^{1}H NMR ($CDCl_3$): δ = 0.88 (d, J = 5.7 Hz, 6 H, Me_2CHCH$_2$CH), 1.62−1.80 (m, 3 H, Me$_2$C*H*CH$_2$CH), 2.71 (m, 2 H, CHC*H*$_2$CH$_2$N), 3.95 (t, J = 9.2 Hz, 2 H, CHCH$_2$C*H*$_2$N), 4.09 (m, 1 H, Me$_2$CHCH$_2$C*H*), 6.08 (t, J = 2.7 Hz, 1 H, C*H*CH$_2$CH$_2$N), 7.32 (s, 1 H, HN). − ^{13}C NMR ($CDCl_3$): δ = 21.4 and 23.1 (Me_2CHCH$_2$CH), 24.4 (Me$_2$*C*HCH$_2$CH), 27.8 (CH*C*H$_2$CH$_2$N), 43.9 (Me$_2$CH*C*H$_2$CH), 45.6 (CHCH$_2$*C*H$_2$N), 55.9 (Me$_2$-CHCH$_2$*C*H), 118.8 (*C*HCH$_2$CH$_2$N), 133.0 (C), 157.7 (C=O), 163.2 (C=O). − MS: *m*/*z* (%) = 209 (17.2) [M$^+$ + 1], 208 (100) [M$^+$], 166 (14.5), 165 (53.9), 152 (10.0), 96 (9.9), 69 (15.4), 68 (14.0), 43 (16.4), 41 (24.3). − HRMS ($C_{11}H_{16}N_2O_2$): calcd. 208.1212; found 208.1213.

3-Benzyl-2,3,6,7-tetrahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (7f): Starting material **6f** (R_f = 0.56), 3 h or 7 h of reflux afforded a mixture of **7f** (25% yield) and racemic ***rac*-6f** (75% yield). **7f:** Colourless needles. − M.p.160−165 °C (EtOAc). − R_f = 0.28 (acetone/$CHCl_3$, 1:2). − ^{1}H NMR($CDCl_3$): δ = 2.59 (m, 2 H, CHC*H*$_2$CH$_2$N), 3.04 (dd, J_1 = 6.8 and J_2 = 13.6 Hz, 1 H, *A*BX, PhC*H*$_2$CH), 3.17 (dd, J_1 = 3.7 and J_2 = 13.6 Hz, 1 H, A*B*X, PhC*H*$_2$CH), 3.87 (m, 2 H, CHCH$_2$C*H*$_2$N), 4.34 (m, PhCH$_2$C*H*), 5.89 (t, J = 2.8 Hz, 1 H, C*H*CH$_2$CH$_2$N), 6.96 (s, 1 H, HN), 7.12 and 7.21 (2 m, 5 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 28.1 (CH*C*H$_2$CH$_2$N), 41.4 (Ph*C*H$_2$CH), 45.7 (CHCH$_2$*C*H$_2$N), 58.9 (PhCH$_2$*C*H), 119.4 (*C*HCH$_2$CH$_2$N), 127.8 (CH$_{Ph}$), 129.1 and 130.2 (4 CH$_{Ph}$), 133.0 (C), 135.2 (C$_{Ph}$), 158.1 (C=O), 162.3 (C=O). − MS: *m*/*z* (%) = 244 (2.3) [M$^+$ + 2], 243 (17.5) [M$^+$ + 1], 242 (100) [M$^+$], 151 (24.9) [M$^+$ − PhCH$_2$], 123 (13.6), 97 (26.2), 91 (89.6) [PhCH$_2$]. − HRMS ($C_{14}H_{14}N_2O_2$): calcd. 242.1055; found 242.1055.

The use of **7f** or **8f** as starting materials gave a mixture of **7f** and racemic ***rac*-6f** (80:20 or 75:23 respectively determined by ^{1}H NMR spectroscopy from the crude material) after 3 h of reflux (see Table 1, entries 8 and 9).

[4+2] Cycloadducts *rac*-12 and *rac*-13: A mixture of the 3-alkylidene-2,5-piperazinedione **6e** (104 mg, 0.5 mmol), 1,1-diphenylethene (540 mg, 3 mmol) and formic acid (8 mL) was refluxed under argon for 6 days. The reaction mixture was concentrated under vacuum and the residue was separated by flash chromatography (EtOAc/hexane, 1:1).

***rac*-12:** Yield 138 mg (71%), colourless crystals. M.p. 246−247 °C (CH_2Cl_2/hexane). − R_f = 0.48 (starting material **6e**: R_f = 0.09). − ^{1}H NMR ($CDCl_3$): δ = 0.48 (m, 1 H, CH$_2$C*H*$_2$CH$_2$C), 0.95 (d, J = 6.2 Hz, 3 H, Me_2CHCH$_2$C), 0.98 (d, J = 6.2 Hz, 3 H, Me_2CHCH$_2$C), 1.50 (m, 1 H, CH$_2$C*H*$_2$CH$_2$C), 1.76–2.00 (m, 4 H, Me$_2$C*H*CH$_2$C and CH$_2$CH$_2$C*H*$_2$C), 2.78 (m, 1 H, C*H*$_2$CH$_2$CH$_2$C), 2.79 (d, J = 14.0 Hz, 1 H, Ph$_2$C−C*H*$_2$), 2.91 (m, 1 H, CH$_2$CH$_2$C*H*$_2$C), 3.01 (d, J = 14.0 Hz, 1 H, Ph$_2$C−C*H*$_2$), 3.13 (m, 1 H, C*H*$_2$CH$_2$CH$_2$C), 6.76 (m, 2 H, CH$_{Ph}$), 7.06 (s, 1 H, HN), 7.12−7.22 (m, 8 H, CH$_{Ph}$). −^{13}C NMR ($CDCl_3$): δ = 23.0 (CH$_2$*C*H$_2$CH$_2$C), 24.0 (Me$_2$*C*HCH$_2$C), 24.3 (Me_2CHCH$_2$C), 24.9 (Me_2CHCH$_2$C), 27.2 (CH$_2$CH$_2$*C*H$_2$C), 39.2 (Me$_2$CH*C*H$_2$C), 44.1 (*C*H$_2$CH$_2$CH$_2$C), 51.1 (Ph$_2$C−CH$_2$), 56.7 (Ph$_2$*C*−CH$_2$), 61.6 (Me$_2$CHCH$_2$*C*), 72.9 (CH$_2$CH$_2$CH$_2$*C*), 126.5 (CH$_{Ph}$), 127.1 (CH$_{Ph}$), 127.8 (CH$_{Ph}$), 128.3 (CH$_{Ph}$), 128.9 (CH$_{Ph}$), 129.6 (CH$_{Ph}$), 144.8 (C$_{Ph}$), 147.4 (C$_{Ph}$), 170.0 (C=O), 173.4 (C=O). − MS: *m*/*z* (%) = 389 (4.1) [M$^+$ + 1], 268 (6.4), 193 (5.7), 178 (32.8), 165 (100). − HRMS ($C_{25}H_{29}N_2O_2$): calcd. 389.2229; found 389.2225 [M$^+$ + 1].

***rac*-13**: Yield 55 mg (28%), colourless needles. M.p. 130 °C (decomposition) (CH_2Cl_2/hexane). − R_f = 0.37. − ^{1}H NMR ($CDCl_3$): δ = 0.69 (d, J = 6.6 Hz, 3 H, Me_2CHCH$_2$C), 0.85 (d, J = 6.6 Hz, 3 H, Me_2CHCH$_2$C), 1.34 (dd, J_1 = 5.9, J_2 = 15.0 Hz, 1 H, Me$_2$CHC*H*$_2$C), 1.64–1.78 (m, 2 H, Me$_2$C*H*CH$_2$C and CH$_2$CH$_2$C*H*$_2$C), 1.93 (m, 2 H, CH$_2$C*H*$_2$CH$_2$C), 2.41 (dd, J_1 = 6.6, J_2 = 15.0 Hz, 1 H, Me$_2$CHC*H*$_2$C), 2.63 (d, J = 14.2 Hz, 1 H, Ph$_2$C−C*H*$_2$),), 2.75 (m, 1 H, CH$_2$CH$_2$C*H*$_2$C), 2.93 (d, J = 14.2 Hz, 1 H, Ph$_2$C−C*H*$_2$), 3.40 (m, 1 H, C*H*$_2$CH$_2$CH$_2$C), 3.51 (m, 1 H, C*H*$_2$CH$_2$CH$_2$C),), 6.15 (s, 1 H, HN), 6.92 (m, 2 H, CH$_{Ph}$), 7.10–7.20 (m, 8 H, CH$_{Ph}$). − ^{13}C NMR ($CDCl_3$): δ = 24.1 (CH$_2$*C*H$_2$CH$_2$C), 24.2 (Me$_2$*C*HCH$_2$C), 24.3 (Me_2CHCH$_2$C), 24.4 (Me_2CHCH$_2$C), 29.1 (CH$_2$CH$_2$*C*H$_2$C), 36.4 (Me$_2$CH*C*H$_2$C), 44.5 (*C*H$_2$CH$_2$CH$_2$C), 51.1 (Ph$_2$C−CH$_2$), 59.7 (Ph$_2$*C*−CH$_2$), 66.4 (CH$_2$CH$_2$CH$_2$*C*), 67.4 (Me$_2$CHCH$_2$*C*), 126.4 (CH$_{Ph}$), 126.8 (CH$_{Ph}$), 127.6 (CH$_{Ph}$), 128.0 (CH$_{Ph}$), 129.1 (CH$_{Ph}$), 130.1 (CH$_{Ph}$), 145.2 (C$_{Ph}$), 147.0 (C$_{Ph}$), 168.3 (C=O), 173.5 (C=O). − MS: *m*/*z* (%) = 389 (1.2) [M$^+$ + 1], 208 (4.3), 189 (4.5), 178 (29.9), 165 (100). − HRMS ($C_{25}H_{29}N_2O_2$): calcd. 389.2229; found 389.2231 [M$^+$ + 1].

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