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Enantioselective synthesis of 2,6-diaminopimelic acid derivatives. Part 3[†]

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Abstract—Enantiomerically pure 2,6-diaminopimelic acid derivatives **9a**–**c** and **10a**–**c** have been synthesized starting from the glycine-derived chiral synthon (1′*S*,1″*S*)-**1**. The absolute configuration of stereocenters introduced on **2** and **3** were assigned on the basis of ^{1}H NMR data and conformational analysis. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

In previous papers[1,2] we have described a new stereoselective approach to both enantiomers of 2,6-diaminopimelic (2,6-DAP) and 2,7-diaminosuberic acids and (*S*,*S*)-*ortho*-phenylene-bis-alanine starting from the homochiral heterocyclic synthon (1′*S*,1″*S*)-**1** already employed by us in the past.

We aim to synthesize enantiomerically pure structural analogues of 2,6-DAP because these derivatives have potential antibacterial and herbicide activity,[3] 2,6-DAP being the penultimate intermediate in the biosynthesis of L-lysine necessary for the growth of Gram positive and many Gram negative bacteria. Structural analogues of 2,6-DAP can inhibit the formation or metabolism of this compound, which lies on the metabolic route to L-lysine, offering promising biological activity. To this end, we recently reported a new stereocontrolled synthesis of uncommon tripeptides, which can be regarded as structural variants of 2,6-DAP, starting from a mono-lactim ether derived from L-valine.[4]

2. Results and discussion

Herein, we wish to report an efficient synthesis of enantiomerically pure bis(α-amino acids) **9** and **10** which can be considered mimics of 2,6-DAP. The synthetic route shown in Scheme 1 is based on the alkylation of the bicyclic intermediates (1*R*,4*R*)-**2** and (1*S*,4*S*)-**3**, obtained in good yields and diastereomeric ratio of 7:3, respectively.[1]

The carbanions of **2** and **3** have been obtained by employing CH_3Li, *n*-C_4H_9Li and *tert*-C_4H_9Li, metallation with LHMDS and *tert*-C_4H_9OK does not occur. The alkylation of (1*R*,4*R*)-**2** occurs almost exclusively at the bridgehead position giving diastereomers **4a**–**c** in good yields (entries 1–5 in Table 1), which can be easily converted into the α-alkyl derivatives of 2,6-DAP **9a**–**c** (Scheme 1). The intermediates **4d** and **8d** cannot be converted into the corresponding bis(α-amino acid) derivatives because the double bond is not resistant to the acidic conditions required for hydrolysis.

While the reaction yield is sensitive to the type of base employed (compare entries 1 and 5), the electrophile used has no effect on the regioselectivity of the alkylation (see entries 1–4). In fact, by treating the substrate (1*R*,4*R*)-**2** with 1.3 equivalents of base, followed by addition of methyl iodide, alkylation at the bridgehead position is accomplished with both CH_3Li and *n*-C_4H_9Li in 80 and 65% yield, respectively.

Conversely, with diastereomer (1*S*,4*S*)-**3**, the reaction exclusively occurs at the competitive benzylic position of the (*S*)-*N*-phenethyl group when 1.3 equivalents of base is employed. In fact, treatment of the substrate **3** with CH_3Li, *n*-C_4H_9Li or *tert*-C_4H_9Li (entries 6, 10 and 12) provides the alkyl derivatives at the benzylic position **6** and **7** in about 40 and 25–30% yields, respectively, the alkylation at the bridgehead not being observed. Thus, it is reasonable to deduce that for the diastereomer (1*S*,4*S*)-**3** the benzylic protons are more acidic than the bridgehead proton. By employing 2.3 or

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[†] References 1 and 2 are considered to be Parts 1 and 2, respectively.

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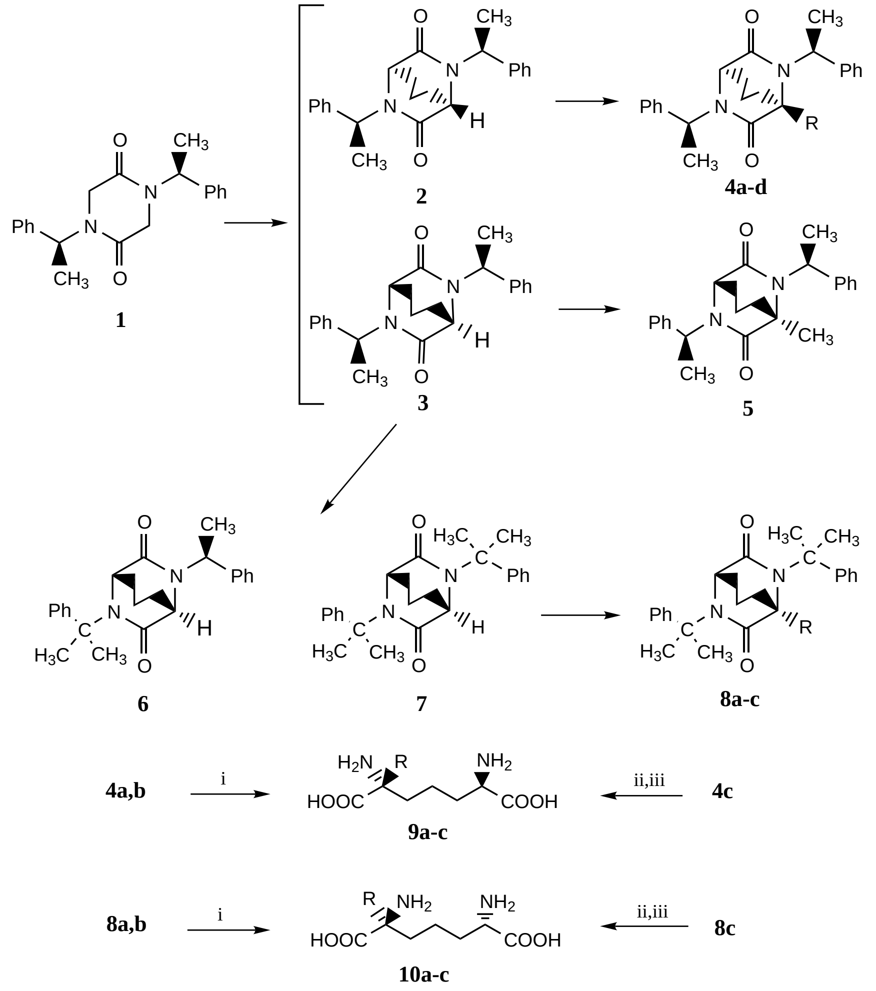

Scheme 1. R = (a) CH_3; (b) CH_2Ph; (c) CH_2OCH_3; (d) CH_2CHCH_2. *Reagents and conditions*: (i) 57% HI at reflux; (ii) Na/NH_3; (iii) 6N HCl at reflux.

Table 1. Alkylation of substrates (1*R*,4*R*)-**2** and (1*S*,4*S*)-**3** under various conditions

Entry	Substrate	Base (equiv.)	R–X (equiv.)	**4** (%)	**5** (%)	**6** (%)	**7** (%)
1	**2**	CH_3Li (1.3)	CH_3I (1.3)[a]	80			
2	**2**	CH_3Li (1.3)	CH_2CHCH_2Br (1.3)	80			
3	**2**	CH_3Li (1.3)	$PhCH_2Br$ (1.3)[a]	80			
4	**2**	CH_3Li (1.3)	CH_3OCH_2Br (1.3)[a]	75			
5	**2**	*n*-C_4H_9Li (1.3)	CH_3I (1.3)	65			
6	**3**	CH_3Li (1.3)	CH_3I (1.3)			40	30
7	**3**	CH_3Li (2.3)	CH_3I (2.3)		30		70
8	**3**	CH_3Li (3.3)	CH_3I (3.3)[b]		15		55
9	**3**	CH_3Li (3.3)	CH_3I (1.3)		45	20	35
10	**3**	*n*-C_4H_9Li (1.3)	CH_3I (1.3)			40	30
11	**3**	*n*-C_4H_9Li (2.3)	CH_3I (2.3)		10		90
12	**3**	*tert*-C_4H_9Li (1.3)	CH_3I (1.3)			40	25

[a,b] The product from alkylation at both the bridgehead and one benzylic position is recovered in about 10% yield[a] and 25% yield[b].

3.3 equivalents of CH_3Li followed by an equimolar amount of CH_3I (entries 7 and 8), the derivative alkylated at the bridgehead position **5** is obtained in 30 or 15% yield, respectively; however, in both the cases the predominant reaction product was **7** in 70 and 55% yields, respectively. If 3.3 equivalents of CH_3Li and 1.3 equivalent of CH_3I are used (entry 9), the methyl derivative **5** is obtained in 45% yield together with both **6** (20% yield) and **7** (35% yield), which are alkylated at the benzylic position.

The product from alkylation at both the bridgehead and one benzylic position is recovered in about 10% (a) and 25% yield (b). It is interesting to emphasize that by employing 2.3 equivalents of n-C_4H_9Li, followed by an equimolar amount of CH_3I (entry 11), a strong increase of derivative **7** is registered (90% yield, along with a 10% yield of **5**).

These findings clearly show that alkylation at the bridgehead carbon can be easily accomplished on the substrate (1*R*,4*R*)-**2**, while its diastereomer (1*S*,4*S*)-**3** is alkylated preferentially at the benzylic position,[5] particularly when a bulky base is employed.[6]

These results can be explained in part by the reasoning suggested by Eastwood[7] for the factors affecting the ability to lithiate the bridgehead position in analogous compounds. Stabilization of a negative charge at the bridgehead position would occur through the following effects.

(a) Dipole stabilization by the partial positive charge on the adjacent amide nitrogen.
(b) Inductive or field effects due to the adjacent carbonyl group.
(c) Orbital overlap with the π-orbital of the carbonyl group.

The last factor depends on the geometry of the molecule because the conjugation of the lone pair at the bridgehead carbon (in an ion pair) is stronger the more coplanar the lone pair is with the π-orbital of the adjacent carbonyl group. Thus, the enolate ion character will be greater the closer the dihedral angle Li–C–C=O is to 90°. Also a little orbital overlap implies a molecular distortion which is very strong in bicyclic systems where the bridge is small and it decreases when the bridge length increases. The competitive acidity of the benzylic protons with respect to that of the bridgehead protons is due to both stabilization of the resulting benzylic anion (electrons of the C–Li bond) by a resonance contribution with the aromatic ring and the opportunity to give rise to a pentatomic cyclic system by means of chelation between the adjacent carbonyl oxygen and the lithium cation.[8]

As already observed for analogous derivatives,[1,2] the conformation where both the benzylic protons of the (*S*)-phenethyl groups are *synperiplanar* to the adjacent carbonyl groups (the heterocyclic ring being in the boat conformation) is energetically preferred.[9] Since the energy calculations show that, as predicted, the dihedral angles Li–C–C=O of (1*R*,4*R*)-**2** and (1*S*,4*S*)-**3** are very similar (about 14 and 10°, respectively), the acidity of the bridgehead proton in **2** and **3** can reasonably be considered the same. Thus, we believe that the better chemical yields of **4** over those of **5** are probably because the bridgehead proton in **2** is less sterically encumbered than in **3** (as can be deduced from an examination of the previously calculated geometries[1]). Additionally, the approach of the electrophile, which occurs from the opposite side of the C_3 bridge, appears more hindered sterically in the carbanion of **3** than in that of **2**. This explanation is supported by the experimental evidence, in that CH_3Li is the only base which allows formation of the alkyl derivative at the bridgehead carbon of diastereomer **3** (entries 7–9 in Table 1). As a consequence of this reduced stereoaccessibility to the bridgehead carbon, preferential attack at the benzylic position of the (*S*)-phenethyl group takes place in the diastereomer **3**.

Finally, it is interesting to note that the intermediate **7**, in addition to **5**, can also be used to obtain the enantiomerically pure α-alkyl derivatives of 2,6-DAP **10a**–**c**. In fact, the derivative **7** can be further alkylated at the bridgehead position to provide **8**, by employing 1.3 equivalents of CH_3Li and an equimolar amount of electrophile. Analogously to **5**, the intermediates **8a**–**c** can subsequently be converted into **10a**–**c** (Scheme 1) following the procedure already reported.[10]

The absolute configuration of the introduced stereocenters of **2** and **3** have been assigned through the ^1H NMR chemical shifts following the methodology already employed.[1,2] The approach is based on the shielding induced by the aromatic ring of the (*S*)-phenethyl group on the bridged chain protons of diastereomer (1*R*,4*R*)-**2** owing to the preferred doubly *synperiplanar* conformation.

3. Conclusion

In conclusion, we have carried out a new and stereoselective approach to the synthesis of enantiomerically pure analogues of 2,6-DAP with potential biological activity[3] (antibacterial and/or herbicide) starting from the chiral heterocyclic synthon **1**, employed previously by us. The synthetic strategy is based on the alkylation of diastereomeric bicyclic intermediates (1*R*,4*R*)-**2** and (1*S*,4*S*)-**3**, easily obtained from **1**, followed by simple cleavage to afford enantiomerically pure α-alkyl derivatives of 2,6-DAP. This strategy is a versatile approach because it allows the preparation of various derivatives of 2,6-DAP mimics, with promising possibilities as specific inhibitors of enzymes along the biosynthetic 'diaminopimelate pathway' leading to L-lysine in bacteria and higher plants.

4. Experimental

4.1. General information

^1H and ^{13}C NMR spectra were recorded on a Gemini spectrometer at 300 MHz using $CDCl_3$ as solvent, unless otherwise stated. Chemical shifts are reported in ppm relative to $CDCl_3$ or to 1,4-dioxane if D_2O is used as solvent. The coupling constants (J) are in Hz. Dry THF was distilled from sodium benzophenone ketyl. Chromatographic separations were performed with silica gel 60 (230–400 mesh). Optical rotation values were measured on a Perkin–Elmer 343 polarimeter.

4.2. (1′*S*)-1,4-Bis-[*N*-1′-phenethyl)]-piperazine-2,5-dione 1

The product was prepared following the procedure reported in Ref. 10.

4.3. (1*R*,4*R*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-2,5-diaza-3,6-dioxo-bicyclo[3,2,2]nonane 2

The product was prepared following the procedure reported in Ref. 2. For NMR spectra and $[\alpha]_D$ value see Ref. 1.

4.4. (1*S*,4*S*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-2,5-diaza-3,6-dioxo-bicyclo[3,2,2]nonane 3

The product was prepared following the procedure reported in Ref. 2. For NMR spectra and $[\alpha]_D$ value see Ref. 1.

4.5. Alkylation of 2 and 3: general procedure

A stirred solution of **2** or **3** (0.8 g, 2.1 mmol) in dry THF (30 mL) cooled to −78°C was treated with base (see Table 1). After about 5 min, the appropriate alkylating reagent (see Table 1) was added and the reaction was then monitored by TLC. When the reaction was practically complete, the mixture was allowed to warm to room temperature with stirring. Dilute aqueous HCl and ethyl acetate were added and after separation, the organic solution was evaporated in vacuo. The residue was purified by silica gel chromatography eluting with hexane/ethyl acetate.

4.5.1. (1*R*,4*R*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-3,6-dioxo-1-methyl-bicyclo[3,2,2]nonane 4a. The product was obtained by alkylating **2** with iodomethane (see entry 1 in Table 1). ^{1}H NMR δ: 0.8–1.8 (m, 6H); 1.51 (d, 3H, *J*=6.9); 1.67 (s, 3H); 1.83 (d, 3H, *J*=7.2); 3.79 (bs, 1H); 5 (m, 1H); 5.96 (q, 1H, *J*=7.2); 7.3 (m, 10ArH). ^{13}C NMR δ: 16.1, 18, 20.9, 23.4, 24.7, 35.7, 51, 52.7, 55.2, 63.6, 125.7, 126.5, 127.7, 127.9, 128, 128.4, 138.8, 141.7, 169.8, 170.2. $[\alpha]_D$ −154.5 (*c* 0.71, $CHCl_3$). Anal. calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.5; N, 7.44. Found: C, 76.79; H, 7.52; N, 7.42%.

4.5.2. (1*S*,4*R*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-1-benzyl-3,6-dioxo-bicyclo[3,2,2]nonane 4b. The product was obtained by alkylating **2** with benzyl bromide (see entry 3 in Table 1). ^{1}H NMR δ: 0.7 (m, 1H); 1.4–1.7 (m, 5H); 1.65 (d, 3H, *J*=7); 1.79 (d, 3H, *J*=7); 3.26 (d, 1H, *J*=16); 3.91 (dd, 1H, *J*=3, 4.8); 4 (d, 1H, *J*=16); 5 (broad, 1H); 6.01 (q, 1H, *J*=7); 6.8–7.5 (m, 15ArH). ^{13}C NMR δ: 16.7, 18.7, 20.6, 25, 34.4, 41.5, 51.4, 54.2, 55.1, 67.7, 125.8, 126, 126.3, 127.4, 128, 128.1, 128.2, 128.6, 130.2, 135.8, 138.9, 141.3, 169.6, 171.2. $[\alpha]_D$ −194.7 (*c* 0.59, $CHCl_3$). Anal. calcd for $C_{30}H_{32}N_2O_2$: C, 79.61; H, 7.13; N, 6.19. Found: C, 79.35; H, 7.15; N, 6.18%.

4.5.3. (1*S*,4*R*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-3,6-dioxo-1-methoxymethyl-bicyclo[3,2,2]nonane 4c. The product was obtained by alkylating **2** with bromomethyl methyl ether (see entry 4 in Table 1). ^{1}H NMR δ: 0.6 (m, 1H); 1.46 (d, 3H, *J*=7); 1.6 (m, 5H); 1.8 (d, 3H, *J*=7); 3.38 (s, 3H); 3.69 (dd, 1H, *J*=3, 4.8); 3.86 (d, 1H, *J*=11.4); 4.02 (d, 1H, *J*=11.4); 4.86 (q, 1H, *J*=7.0); 5.95 (q, 1H, *J*=7); 7.3 (m, 10ArH). ^{13}C NMR δ: 16, 16.9, 20.3, 24.8, 30.1, 50.5, 53.7, 54.9, 58.8, 66, 73.2, 125.6, 125.9, 127.6, 127.8, 128.3, 138.7, 142.3, 168.2, 169.7. $[\alpha]_D$ −191.3 (*c* 1.15, $CHCl_3$). Anal. calcd for $C_{25}H_{30}N_2O_3$: C, 73.86; H, 7.44; N, 6.89. Found: C, 73.88; H, 7.46; N, 6.92%.

4.5.4. (1*S*,4*R*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-1-allyl-3,6-dioxo-bicyclo[3,2,2]nonane 4d. The product was obtained by alkylating **2** with allyl bromide (see entry 2 in Table 1). ^{1}H NMR δ: 0.7 (m, 1H); 1.53 (d, 3H, *J*=7); 1.4–2 (m, 5H); 1.83 (d, 3H, *J*=7); 2.89 (dd, 1H, *J*=7.8, 16); 3.08 (dd, 1H, *J*=5.6, 16); 3.76 (dd, 1H, *J*=3.4, 4.8 Hz); 4.96 (q, 1H, *J*=7); 5.05–5.2 (m, 2H); 5.9–6.15 (m, 2H); 7.2–7.45 (m, 10ArH). ^{13}C NMR δ: 16.3, 17.4, 20.8, 24.9, 34.5, 40.7, 50.9, 53, 55, 65.6, 118.7, 125.5, 126.1, 127.8, 128, 128.5, 133.5, 138.9, 141.8, 169.2, 170.6. $[\alpha]_D$ −182.7 (*c* 0.79, $CHCl_3$). Anal. calcd for $C_{26}H_{30}N_2O_2$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.45; H, 7.48; N, 6.97%.

4.5.5. (1*S*,4*S*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-3,6-dioxo-1-methyl-bicyclo[3,2,2]nonane 5. The product was obtained by alkylating **3** with iodomethane (see entry 9 in Table 1). ^{1}H NMR δ 1.38 (bs, 3H); 1.57 (d, 3H, *J*=7.2); 1.6–2 (m, 6H); 1.74 (d, 3H, *J*=7.2); 3.83 (bs, 1H); 5.6–6 (bs, 1H); 5.88 (q, 1H, *J*=7.2); 7.17–7.4 (m, 10ArH). ^{13}C NMR δ: 16.8, 18.1, 21.4, 23.3, 27, 36.3, 51.2 (broad), 55.4, 63.6, 126.8, 126.9, 128, 128.4, 128.8, 140.2, 142.2, 170.5, 170.9. $[\alpha]_D$ −39 (*c* 0.51, $CHCl_3$). Anal. calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.5; N, 7.44. Found: C, 76.79; H, 7.52; N, 7.42%.

4.5.6. (1*S*,4*S*,1′*S*)-2-*N*-(1′-Phenethyl)-5-*N*-(1″-phenylisopropyl)-3,6-dioxo-bicyclo[3,2,2]nonane 6. The product was obtained by alkylating **3** with iodomethane (see entry 6 or 10 in Table 1). After chromatographic separation the product was not isolated in pure enough form to measure the specific rotation and to obtain satisfactory elemental analysis. ^{1}H NMR δ: 1.57 (d, 3H, *J*=7.2); 1.6–2.05 (m, 6H); 1.66 (s, 3H); 1.85 (s, 3H); 3.65 (t, 1H, *J*=4); 4.28 (t, 1H, *J*=4); 5.83 (q, 1H, *J*=7.2); 7.3 (m, 10ArH); ^{13}C NMR δ: 17, 20, 26.6, 26.9, 27.1, 29.8, 50.4, 56.9, 57.8, 62, 124.6, 126.6, 126.8, 127.8, 128.3, 128.7, 139.9, 146.5, 169, 169.6.

4.5.7. (1*S*,4*S*)-2,5-Bis-[*N*-(1′-phenylisopropyl)]-3,6-dioxo-bicyclo[3,2,2]nonane 7. The product was obtained by alkylating **3** with iodomethane (see entry 11 in Table 1). ^{1}H NMR δ: 1.64 (s, 6H); 1.6–2.1 (m, 6H); 1.91 (s, 6H); 4.1 (t, 2H, *J*=6); 7.3 (m, 10ArH). ^{13}C NMR δ: 19.8, 26.7, 29.8, 59.1, 61.5, 124.4, 126.6, 128.1, 146.5, 169.2. $[\alpha]_D$ 166.7 (*c* 0.66, $CHCl_3$). Anal. calcd for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.09; H, 7.75; N, 7.2%.

4.6. Alkylation of 7: general procedure

To a stirred solution of **7** (0.4 g, 1.02 mmol) in dry THF (15 mL) cooled to −55°C was added a solution of CH_3Li in diethyl ether (1.4 M, 0.9 mL). After about 5 min the appropriate alkylating reagent (2 mmol) was added and the reaction was then monitored by TLC. When the reaction was practically complete, the mixture was allowed to warm to room temperature with stirring. Dilute aqueous HCl and ethyl acetate were added and after separation the organic solution was evaporated in vacuo. The residue was purified by silica gel chromatography eluting with hexane/ethyl acetate.

4.6.1. (1*S*,4*S*)-2,5-Bis-[*N*-(1′-phenylisopropyl)]-3,6-dioxo-1-methyl-bicyclo[3,2,2]nonane 8a. Iodomethane was used as alkylating reagent. The product was isolated in 70% yield, the remaining 30% being starting material. ^1H NMR δ: 0.86 (s, 3H); 1.66 (s, 3H); 1.6–2.2 (m, 6H); 1.9 (s, 3H); 1.92 (s, 3H); 1.99 (s, 3H); 4.44 (t, 1H, $J=5.4$); 7.1–7.45 (m, 10ArH). ^{13}C NMR δ: 21.4, 25.7, 26.5, 27.6, 27.9, 30, 35.5, 39, 59.2, 61.2, 65.1, 65.8, 123.8, 124.3, 126.3, 126.4, 128.1, 128.4, 147.4, 149.7, 169.7, 173.7. $[\alpha]_D$ 132.2 (*c* 0.5, $CHCl_3$). Anal. calcd for $C_{26}H_{32}N_2O_2$: C, 77.19; H, 7.97; N, 6.92. Found: C, 76.95; H, 7.95; N, 6.9%.

4.6.2. (1*R*,4*S*)-2,5-Bis-[*N*-(1′-phenylisopropyl)]-1-benzyl-3,6-dioxo-bicyclo[3,2,2]nonane 8b. Benzyl bromide was used as alkylating reagent. The product was isolated in 55% yield along with 25% of starting material and an unidentified by-product. ^1H NMR δ: 1.6–2.2 (m, 6H); 1.74 (s, 3H); 1.85 (s, 3H); 1.94 (s, 6H); 3.05 (q_{AB}, 2H, $J=15$); 4.42 (t, 1H, $J=4$); 6.95–7.5 (m, 15ArH). ^{13}C NMR δ: 21.2, 26.8, 27.6, 29, 34.7, 35.1, 41.5, 59.2, 61.5, 65.7, 69.1, 124, 124.5, 125.9, 126.2, 126.5, 127.7, 128.2, 128.3, 130.8, 138, 147.1, 149.8, 169.1, 172.8. $[\alpha]_D$ 69 (*c* 1.37, $CHCl_3$). Anal. calcd for $C_{32}H_{36}N_2O_2$: C, 79.96; H, 7.55; N, 5.83. Found: C, 80.15; H, 7.57; N, 5.85%.

4.6.3. (1*R*,4*S*)-2,5-Bis-[*N*-(1′-phenylisopropyl)]-3,6-dioxo-1-methoxymethyl-bicyclo[3,2,2]nonane 8c. Bromomethyl methyl ether was used as alkylating reagent. The product was isolated in 80% yield, the remaining 20% being starting material. ^1H NMR (CD_3OD, at 50°C) δ: 1.62 (s, 3H); 1.9 (s, 6H); 1.93 (s, 3H); 1.6–2 (m, 6H); 3.04 (s, 3H); 3.3 (broad, 2H); 4.2 (broad, 1H); 7.1–7.6 (m, 10ArH). ^{13}C NMR δ: 20.8, 24.1 (broad), 26.3, 26.8 (broad), 29.6, 34.6 (broad), 57.7, 58.5 (broad), 61.3 (broad), 65.4 (broad), 67 (broad), 73.2 (broad), 124.1, 124.3, 125.8, 126.4, 127.5, 128, 146.9, 148.8 (broad), 168. $[\alpha]_D$ 165.7 (*c* 2.47, $CHCl_3$). Anal. calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45. Found: C, 74.6; H, 7.92; N, 6.48%.

4.7. Conversion of 4a,b into 9a,b and 8a,b into 10a,b: general procedure

A solution of compound **4a**,**b** or **8a**,**b** (1 mmol) in 57% HI (5 mL) was heated under reflux.[10] After about 8 h, the reaction mixture was evaporated in vacuo, the residue was dissolved in water (5 mL) and the solution was adsorbed on ion-exchange resin Amberlist H 15. The resin was washed with methanol then distilled water and eluted with 5 M NH_4OH to recover the enantiomerically pure 2,6-DAP derivatives **9a**,**b** or **10a**,**b**.

4.7.1. (2*R*,6*R*)-2-Methyl-2,6-diaminopimelic acid 9a. The product was obtained from **4a** in 88% yield. ^1H NMR (D_2O) δ: 1.3–1.5 (m, 2H); 1.49 (s, 3H); 1.7–2 (m, 4H); 3.95 (t, 1H, $J=6$). ^{13}C NMR (D_2O) δ: 19.7, 20.2, 30.1, 36.7, 53.1, 60.5, 171.2, 174.2. $[\alpha]_D$ −28.2 (*c* 0.75, 1N HCl). Anal. calcd for $C_8H_{16}N_2O_4$: C, 47.05; H, 7.9; N, 13.72. Found: C, 47.15; H, 7.95; N, 13.7%.

4.7.2. (2*S*,6*S*)-2-Methyl-2,6-diaminopimelic acid 10a. The product was obtained from **8a** in 90% yield. $[\alpha]_D$ 28 (*c* 0.534, 1N HCl).

4.7.3. (2*S*,6*R*)-2-Benzyl-2,6-diaminopimelic acid 9b. The product was obtained from **4b** in 90% yield. ^1H NMR (D_2O) δ: 1.2–1.6 (m, 2H); 1.7–2.1 (m, 4H); 2.96 (d, 1H, $J=14.6$); 3.25 (d, 1H, $J=14.6$); 3.94 (t, 1H, $J=6.2$); 7.3 (m, 5ArH). ^{13}C NMR (D_2O) δ: 19.7, 30.2, 35.5, 41.8, 53.1, 64.7, 128.9, 129.8, 130.8, 133.2, 172, 173. $[\alpha]_D$ −11.7 (*c* 0.6, 1N HCl). Anal. calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 60.13; H, 7.2; N, 10.02%.

4.7.4. (2*R*,6*S*)-2-Benzyl-2,6-diaminopimelic acid 10b. The product was obtained from **8b** in 92% yield. $[\alpha]_D$ 11.5 (*c* 0.71, 1N HCl).

4.8. Conversion of 4c into 9c and 8c into 10c: general procedure

Under an inert atmosphere, a solution of **4c** or **8c** (1.2 mmol) in dry THF (10 mL) and ethanol (1 mL) was added to a stirred solution of Na (0.2 g, 8.7 mmol) in liquid ammonia (about 30 mL) cooled to −60°C. After 5 min the reaction was quenched with 0.5 g of NH_4Cl and the cooling bath was removed allowing complete removal of NH_3. Water was added and the solution was extracted with ethyl acetate. The product was recovered in good yield after purification by silica gel chromatography eluting with hexane/ethyl acetate.

4.8.1. (1*S*,4*R*)- or (1*R*,4*S*)-2,5-Diaza-3,6-dioxo-1-methoxymethyl-bicyclo[3,2,2]nonane. ^1H NMR (CD_3OD) δ: 1.6–1.95 (m, 6H), 3.4 (s, 3H), 3.43 (d, 1H, $J=9.6$), 3.7 (d, 1H, $J=9.6$), 3.77 (m, 1H); ^{13}C NMR (CD_3OD) δ: 21.5, 27, 30.6, 55.6, 59.5, 61.4, 74.1, 174.3.

The pure intermediate (1 mmol) was then heated under reflux for 12 h in 6N aqueous HCl (15 mL). The acid solution was adsorbed on ion-exchange resin Amberlist H 15 and then eluted with 5 M NH_4OH to recover the enantiomerically pure 2,6-DAP derivative **9c** or **10c**.

4.8.2. (2*S*,6*R*)-2-Methoxymethyl-2,6-diaminopimelic acid 9c. The product was obtained from **4c** in 82% overall yield. ^1H NMR (D_2O) δ: 1.2–1.6 (m, 2H); 1.7–2.0 (m, 4H); 3.25 (s, 3H); 3.51 (d, 1H, $J=10.4$); 3.78 (d, 1H, $J=10.4$); 3.95 (t, 1H, $J=6.2$). ^{13}C NMR (D_2O) δ: 19.3, 30.1, 32.1, 53, 59.8, 64.3, 73.9, 172.2, 172.3. $[\alpha]_D$ −19.4

(*c* 0.68, 1N HCl). Anal. calcd for $C_9H_{18}N_2O_5$: C, 46.15; H, 7.75; N, 11.96. Found: C, 46.28; H, 7.77; N, 11.92%.

4.8.3. (2*R*,6*S*)-2-Methoxymethyl-2,6-diaminopimelic acid 10c. The product was obtained from **8c** in 80% overall yield. $[\alpha]_D$ 19.1 (*c* 0.7, 1N HCl).

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References

1. Paradisi, F.; Porzi, G.; Rinaldi, S.; Sandri, S. *Tetrahedron: Asymmetry* **2000**, *11*, 1259.
2. Paradisi, F.; Porzi, G.; Rinaldi, S.; Sandri, S. *Tetrahedron: Asymmetry* **2000**, *11*, 4617.
3. (a) Cox, R. J. *Nat. Prod. Rep.* **1996**, *13*, 29; (b) Williams, R. M.; et al. *Tetrahedron* **1996**, *52*, 1149; (c) Williams, R. M.; Yuan, C. *J. Org. Chem.* **1992**, *57*, 6519; (d) Gelb, M. H.; et al. *J. Am. Chem. Soc.* **1990**, *112*, 4932; (e) Vederas, J. C.; et al. *J. Biol. Chem.* **1986**, *261*, 13216; (f) Vederas, J. C.; et al. *J. Biol. Chem.* **1988**, *263*, 11814; (g) Schar, H. P.; et al. *Plant Physiol.* **1992**, *98*, 813.
4. Paradisi, F.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **2001**, *12*, 3319.
5. Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561.
6. (a) Keresztes, I.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 10228; (b) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H. R. *J. Am. Chem. Soc.* **1985**, *107*, 1810; (c) Al-Aseer, M. A.; Smith, S. G. *J. Org. Chem.* **1984**, *49*, 2608.
7. Eastowood, F. W.; Gunawardana, D.; Wernert, G. T. *Aust. J. Chem.* **1982**, *35*, 2289.
8. (a) Iula, D. M.; Gawley, R. E. *J. Org. Chem.* **2000**, *65*, 6196; (b) Gawley, R. E.; Low, E.; Zhang, Q.; Harris, R. *J. Am. Chem. Soc.* **2000**, *122*, 3344.
9. Performed by the AM1 method (HyperChem program 1994) by using the 'Polak-Ribiere algorithm' (RMS gradient 0.01 Kcal).
10. Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **1994**, *5*, 453.