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TETRAHEDRON: *ASYMMETRY*

# A simple asymmetric synthesis of (+)- and (–)-2,6-diaminopimelic acids

Francesca Paradisi, Gianni Porzi,* Samuele Rinaldi and Sergio Sandri*

*Dipartimento di Chimica 'G.Ciamician', Università degli Studi di Bologna, Via Selmi 2, 40126 Bologna, Italy*

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**Abstract**

The asymmetric synthesis of both the enantiomers of 2,6-diaminopimelic acid (2,6-DAP) has been accomplished starting from the chiral synthon **1**. 

(2*S*,6*S*)-2,6-Diaminopimelic acid **6**, biosynthesized in bacteria from pyruvate and aspartate, is the penultimate precursor of L-lysine in the metabolic process necessary for the growth of Gram positive and many Gram negative bacteria. In addition, *meso*-2,6-diaminopimelic acid [(*R*,*S*)-DAP] functions as a cross-linking constituent of the peptidoglycan cell wall layer in bacteria. Because mammals lack this biosynthetic pathway, specific inhibitors of the enzymes along this metabolic route should potentially display antibacterial activity.[1] Hence, in recent years the stereoselective synthesis of several DAP analogues with potential therapeutic effects has received considerable attention.[2]

Owing to our interest directed at the asymmetric synthesis of common and uncommon α-amino acids,[3] we have recently focused our attention on a new stereoselective process to both the enantiomers **5** and **6** of 2,6-DAP. Our simple synthetic approach involves the use of the glycine derived chiral synthon **1** (Scheme 1) which we have already used and can be achieved in good yield starting from (*S*)-α-phenylethylamine.[4] The intermediate **2**[5] was obtained in about 90% yield by alkylating the lithium enolate of **1** with an equimolar amount of 1,3-diiodopropane, according to the previously reported procedure.[4] The diastereomeric mixture of **2** was converted in good yield into the corresponding lithium enolates then cyclized to a 7:3 diastereomeric mixture of bicyclic derivatives[6] (1*R*,4*R*)-**3** and (1*S*,4*S*)-**4**. These intermediates, easily separated by chromatography on silica gel, were then submitted to cleavage with 57% HI (Scheme 1) and the enantiomerically pure 2,6-DAPs,[7] (2*R*,6*R*)-**5** and (2*S*,6*S*)-**6**, were recovered pure after adsorption on Amberlist H-15 ion exchange resin following the protocol already described.[8]

* Corresponding authors. E-mail: porzi@ciam.unibo.it

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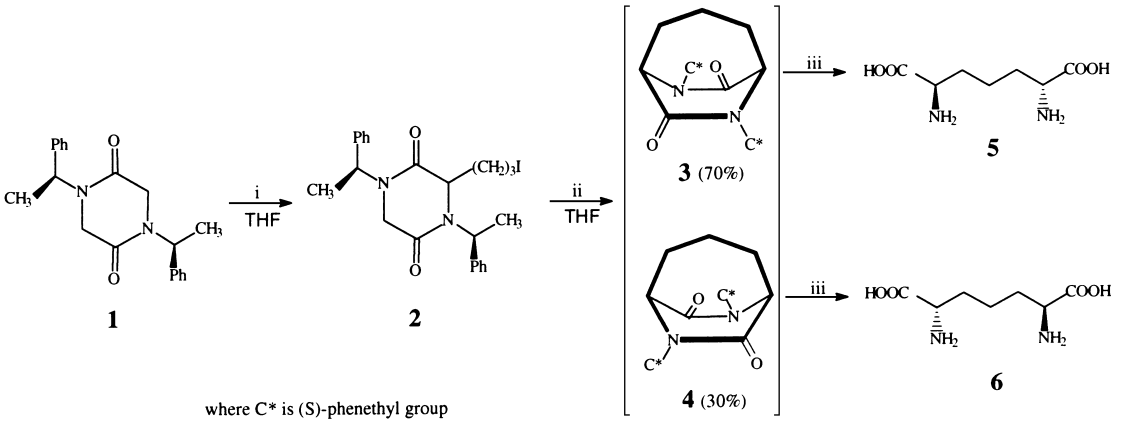


Scheme 1. (i) LHDMS at –10°C, then $I(CH_2)_3I$ at –78°C; (ii) LHDMS at –10°C; (iii) refluxing 57% HI, then adsorption on Amberlist H-15 ion exchange resin and elution with 5 M $NH_4OH$[7]

The absolute configurations of the introduced stereocenters of **3** and **4** were determined following the approach often employed for similar molecules.[8] Actually, as has been previously observed for analogous compounds, the $^1H$ NMR spectra can be explained on the basis of phenyl shielding effects which take place exclusively in those conformers where the benzylic hydrogen of the (*S*)-phenethyl group is synperiplanar with respect to the carbonyl group with the heterocyclic ring being in a boat conformation.[8] The conformational analysis[9] performed on both (1*R*,4*R*)-**3** and (1*S*,4*S*)-**4** showed that doubly synperiplanar conformers are more stable than those which are doubly antiperiplanar by 1.6 kcal/mol and 1.1 kcal/mol, respectively (Fig. 1). In addition, in both isomers **3** and **4** the conformation with one phenethyl group synperiplanar and the other antiperiplanar is 0.8 and 0.5 kcal/mol, respectively, less stable than the doubly synperiplanar conformer. In the present case the *R* configuration of the new stereocenters introduced in **3** was established on the basis of the remarkable upfield shift suffered by the six protons of the $C_3$

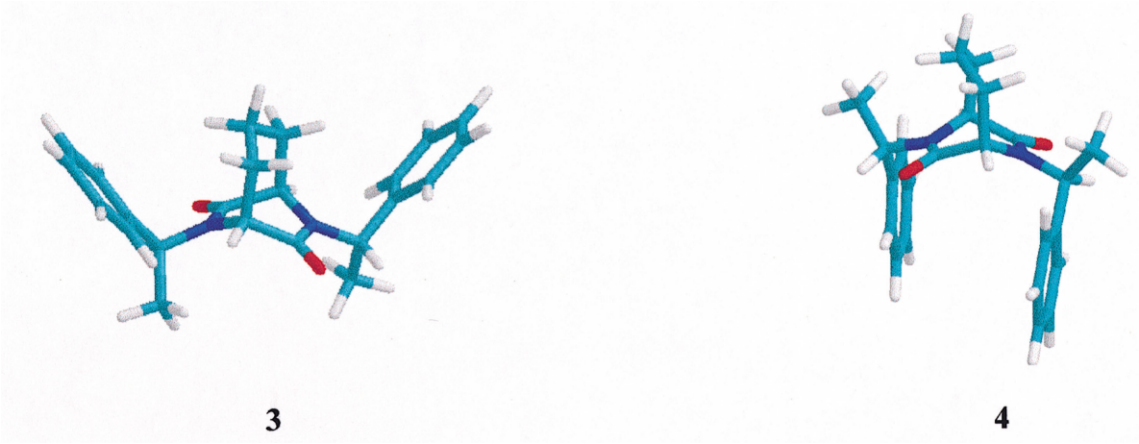


Figure 1. Preferred conformations[9] of isomers **3** and **4**: in the former the shielding exerted by the phenyl ring on the six protons of the $C_3$ bridged chain is shown

bridged chain. Actually, these protons in isomer **4** absorb in the range 1.65–2.05 ppm, while in **3** they resonate at higher fields, i.e. 0.6–1.4 ppm. This upfield shift registered in isomer **3** is ascribable to the phenyl ring of the (*S*)-phenethyl moiety which, in the preferred synperiplanar conformation, can exert a strong shield only on the six protons of the $C_3$ bridged chain, as shown in Fig. 1.

Nevertheless, the assigned configuration of the introduced stereocenters was unequivocally confirmed by converting stereoisomers **3** and **4** into the corresponding (*R*,*R*)-(**5**) and (*S*,*S*)-(**6**) diaminopimelic acids, as reported in Scheme 1. The specific rotation values measured, $[\alpha]_D = -42.5$ (c 1, 1N HCl) for **5** and $[\alpha]_D = +42.1$ (c 0.96, 1N HCl) for **6**, are in good agreement with those reported in the literature.[10]

Further investigations are in progress in order to develop a general methodology applicable to the 2,6-diaminopimelic acid family of amino acids with potential antimicrobial activity.

## Acknowledgements

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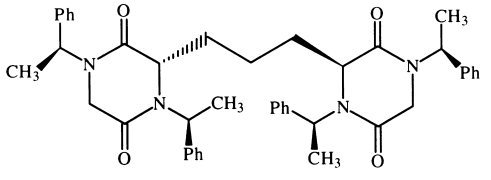
5. After chromatography of the crude reaction (eluting with hexane/ethyl acetate) in addition to the 1,3-diiodopropane the byproduct **7** was isolated in about 10% yield, while the separation of diastereomers of **2** was unsuccessful. However, the subsequent cyclization reaction[6] leads to easily separable diastereomers **3** and **4**. The structure of **7** was determined by $^1$H NMR spectroscopic data and further corroborated by smooth conversion into **6** with refluxing 57% HI. (1′*S*,2*S*)-1,3-Bis-[1,4-*N*,*N*-(1′-phenethyl)-3,6-diketopiperazin-2-yl]-propane **7**: $^1$H NMR $\delta$ ($CDCl_3$) 1.5 (d, 6H, J = 7.2 Hz), 1.6 (d, 6H, J = 7.2 Hz), 1.6 (m, 2H), 1.85 (m, 4H), 3.56 (d, 2H, J = 17.4 Hz), 3.68 (dd, 2H, J = 4.5, 8.4 Hz), 3.94 (d, 2H, J = 17.4 Hz), 5.78 (q, 2H, J = 7.2 Hz), 5.8 (q, 2H, J = 7.2 Hz), 7.3 (m, 20ArH); $^{13}$C NMR $\delta$ ($CDCl_3$) 15.2, 17.3, 21, 33.1, 44.4, 49.7, 51.8, 56.8, 126.8, 127.8, 127.9, 128.6, 128.7, 138.5, 138.9, 165, 165.9; $[\alpha]_D$ –176.1 (c 1.01, $CHCl_3$).




**7**

6. Procedure for the preparation of diastereomers **3** and **4**. To 1.34 g (2.73 mmol) of the diastereomeric mixture of **2** (purified by chromatographic separation of the 1,3-diiodopropane and the byproduct **7**), dissolved in dry THF (100 mL) at –10°C, 2.8 mL (1 M solution in THF) of LHMDS (2.8 mmol), in 10 mL of dry THF, were slowly added. After a few minutes the cooling bath was removed allowing the reaction mixture to warm up to room temperature. Then, diluted HCl was added, the mixture extracted with ethyl acetate and the organic solution evaporated in vacuo. The residue was submitted to silica gel chromatographic separation eluting with hexane/ethyl acetate. The diastereomers **3** and **4** were isolated pure in 70% yield. (1′*S*,1″*S*,1*R*,4*R*)-2,5-Bis-[2,5-*N*,*N*-(1′-phenethyl)]-3,6-dioxo-2,5-diazabicyclo[3,2,2]nonane **3**: $^1$H NMR $\delta$ ($CDCl_3$) 0.6 (m, 2H), 1.22 (m, 2H), 1.4 (m, 2H), 1.52 (d, 6H, J = 6.9 Hz), 3.89 (t, 2H, J = 4 Hz), 5.82 (q, 2H, J = 6.9 Hz), 7.3 (m, 10ArH); $^{13}$C NMR $\delta$ ($CDCl_3$) 16.2, 19.8, 24.8, 50.4, 55.1, 127.8, 128.1, 128.6, 138.8, 169.1; mp 213–215°C; $[\alpha]_D$ –300.9 (c 1.016, $CHCl_3$). (1′*S*,1″*S*,1*S*,4*S*)-2,5-bis-[2,5-*N*,*N*-(1′-phenethyl)]-3,6-dioxo-2,5-diazabicyclo[3,2,2]nonane **4**: $^1$H NMR $\delta$ ($CDCl_3$) 1.53 (d, 6H, J = 7.2 Hz), 1.75 (m, 6H), 1.95 (m, 2H), 3.81 (t, 2H, J = 3.9 Hz), 5.73 (q, 2H, J = 7.2 Hz), 7.15 (m, 4ArH), 7.3 (m, 6ArH); $^{13}$C NMR $\delta$ ($CDCl_3$) 16.5, 20.1, 26.6, 50.1, 55.2, 126.5, 127.7, 128.5, 139.6, 168.8; mp 143–145°C; $[\alpha]_D$ –167.6 (c 1.004, $CHCl_3$).
7. $^1$H NMR $\delta$ ($D_2O$ vs DSS) 1.4 (m, 2H), 1.8 (m, 4H), 3.7 (m, 2H).
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9. Energy calculations were performed by the AM1 method (HyperChem Program, 1994) using the 'Polak-Ribiere algorithm' (RMS gradient 0.01 kcal).
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