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TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of α,α′-diamino-dicarboxylic acids. Part 2†

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Abstract

Enantiomerically pure α,α′-diamino-dicarboxylic acids (*R*,*R*)-**4**, (*S*,*S*)-**5** and (*S*,*S*)-**7** have been synthesized starting from the glycine-derived chiral synthon (*S*,*S*)-**1**.

1. Introduction

In a continuation of our program aimed at the stereoselective synthesis of naturally and non-naturally occurring amino acids,[1] we have recently focused our attention on a new synthetic approach to α,α′-diamino-dicarboxylic acids, which could be useful structural variants of 2,6-diaminopimelic acid (penultimate intermediate in the metabolic process to peptidoglycan and L-lysine for the growth of Gram(+) and many Gram(−) bacteria). In fact, because mammals lack this biosynthetic pathway, aromatic and non-aromatic α,α′-diamino-dicarboxylic acids have received much attention in recent years for their potential antibacterial activity.[2] The interest in such compounds is also motivated by the possibility of incorporating them into biologically active peptides: for instance, the disulfide linkage of cystine in peptoid bioorganics, where it mainly exerts a structural skeletal function, can be replaced by a C_2 unit.[3]

Recently, we reported a new and simple asymmetric synthesis of (+)- and (−)-2,6-diaminopimelic acids[4] accomplished by using the glycine-derived heterocyclic synthon (*S*,*S*)-**1**.

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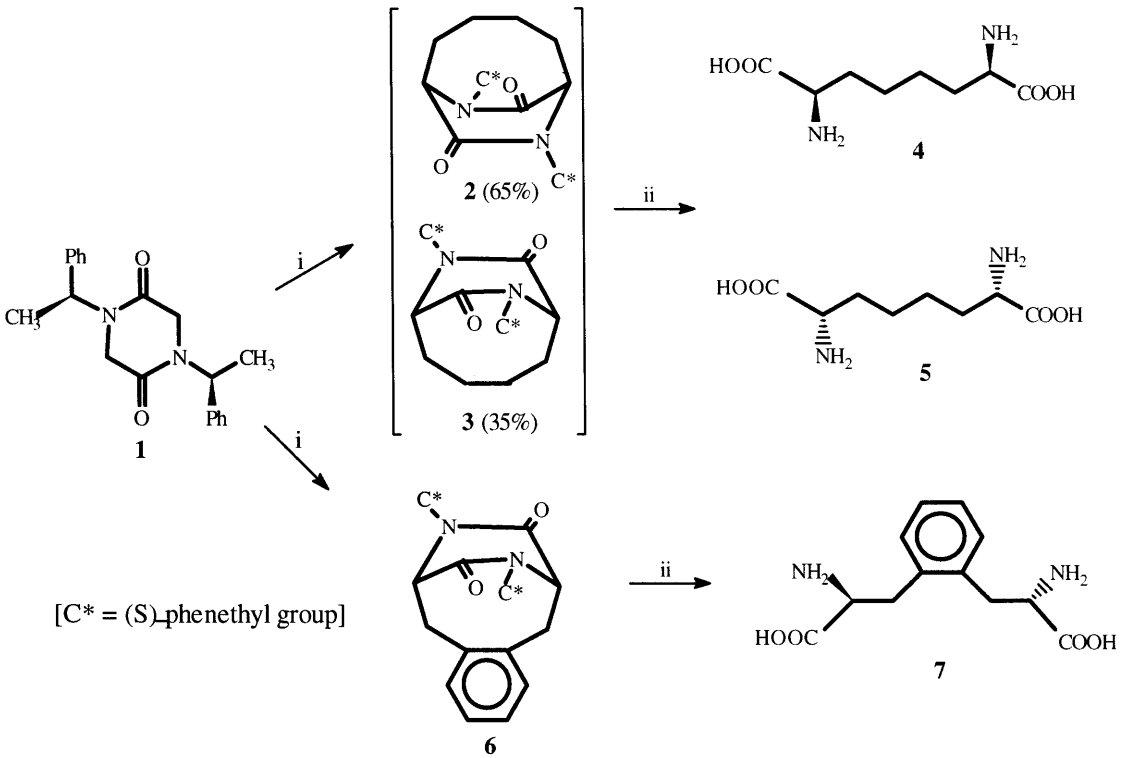
2. Results and discussion

In the present study our efforts have been directed towards producing enantiomerically pure α,α′-diamino-dicarboxylic acids, 2,7-diaminosuberic acid (2*R*,7*R*)-**4** and (2*S*,7*S*)-**5** and (*S*,*S*)-*ortho*-phenylene-bis-alanine **7**, which can be considered structural analogs of 2,6-diaminopimelic acid. The methodology followed is based on the alkylation of the enolate of homochiral synthon **1** with an equimolar amount of the appropriate dihalo-derivative and subsequent base-induced cyclization to the bicyclic intermediates **2**, **3** and **6**, which are easily purified by chromatography on silica gel and smoothly cleaved with 57% HI. The enantiomerically pure α,α′-diamino-diacids (2*R*,7*R*)-**4**, (2*S*,7*S*)-**5** and (*S*,*S*)-**7**, respectively, were then recovered pure in quantitative yield after adsorption on Amberlist H-15 ion-exchange resin following the protocol already used[4] by us (Scheme 1).



Scheme 1. (i) 1.1 equiv. of base at −10°C, then 1 equiv. of the appropriate dihalo-derivative followed by 1.1 equiv. of base at −78°C and chromatographic separation; (ii) refluxing 57% HI, then adsorption on Amberlist H-15 ion-exchange resin and elution with 5 M NH_4OH[4]

While the bicyclic intermediates (1*R*,4*R*)-**2** and (1*S*,4*S*)-**3** were obtained in a 65:35 diastereomeric mixture (de = 30%), respectively, the derivative (1*S*,10*S*)-**6** was recovered as a single stereoisomer in a practically quantitative yield, i.e. the reaction is totally diastereoselective.

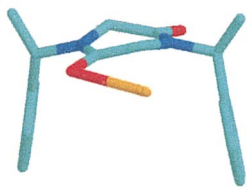
In order to obtain the best results, different bases, such as Li-, Na- and K-bis(trimethylsilyl)amide, were tested by using 1,4-diiodobutane as the electrophile. While the sodium-enolate of **1** gave a mixture of (*R*,*S*)- and (*S*,*S*)-monoiodobutyl-derivatives of **1** (precursors of **2** and **3**) in

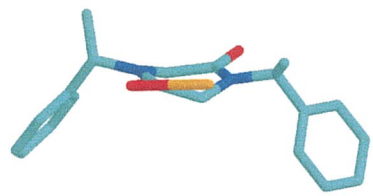
a 65:35 ratio, respectively, 30% de with the lithium-enolate reaction was non diastereoselective (de = 0) (the diastereomeric ratios being ascertained by ^{1}H NMR). The subsequent addition of a second equivalent of base converted the monoiodobutyl-derivatives of **1** into a mixture of **2** and **3**. In contrast, when K-bis(trimethylsilyl)amide was employed the bicyclic compounds **2** and **3** were obtained directly with no diastereoselectivity (de = 0) and the addition of a second equivalent of base converted the remaining starting material **1** into **2** and **3**. Considering that the chromatographic separation of diastereomeric monoiodobutyl-derivatives was unsuccessful, the formation of **2** and **3** can be accomplished in only one step, i.e. without isolating the monoiodobutyl intermediates.

However, independent of the base used, about 10% of the dialkyl byproduct (1′*S*,2*S*)-1,4-bis-[1,4-*N*,*N*-(1′-phenethyl)-3,6-diketopiperazin-2-yl]butane was isolated, consistent with previous observations with 13-diiodopropane.[4]

The best chemical yields (90%) of **6** were registered by employing α,α′-dibromo-*o*-xylene as the electrophile and Li-bis(trimethylsilyl)amide as the base. However, it is interesting that when one equivalent of the base was used the reaction did not give the intermediate monobromoalkyl-derivative of **1** in appreciable amounts, but rather gave the bicyclic compound **6** along with the starting material **1**. Because the formation of **6** was noticed by TLC analysis from the beginning of reaction, the one-step procedure was tried by adding one equivalent of base to **1**, then the α,α′-dibromo-*o*-xylene and again a second equivalent of base, as described for **2** and **3**. By this simple protocol very good chemical yields were achieved and similar results have also been obtained by using α,α′-dichloro-*o*-xylene and K-bis(trimethylsilyl)amide.

8a



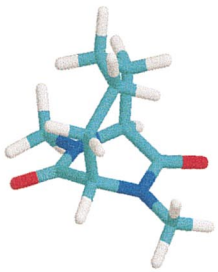
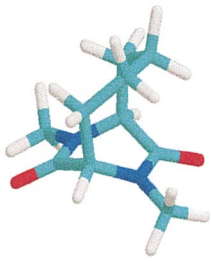


8b

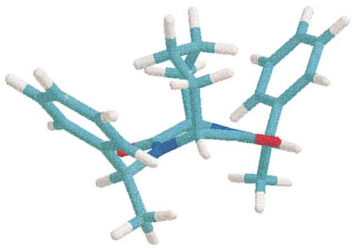
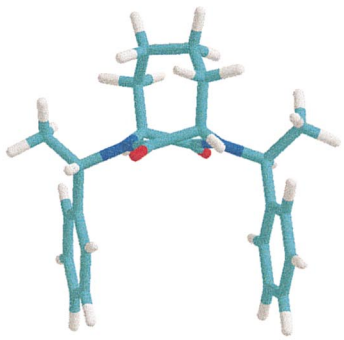
In order to explain the stereochemical results observed, a conformational analysis of the lithium-enolate of **1** was performed[5] showing the conformation **8a** to be slightly more stable (about 2 kcal/mol) than **8b** (the hydrogen atoms are omitted for clarity). Conformer **8a** should induce the approach of the electrophile to the *re* face of the lithium-enolate (which is shielded by the phenyl rings of the (*S*)-phenethyl group) leading to the (*R*)-diastereomer. In contrast, conformer **8b** should bring the electrophile onto the *si* face, affording the (*S*)-diastereomer. The total stereocontrol observed on the bicyclic product (1*S*,10*S*)-**6** might be rationalized by considering that the sterically demanding α,α′-dibromo-*o*-xylene is forced to attack on the *si* face of **8b** instead of the sterically encumbered *re* face of **8a**. Besides, the stereochemical outcome might also be explained by supposing that the ring closure to the bicyclic compound **6** occurs with an entropic gain due to the conformationally rigid electrophile used: in fact, as reported above, the formation of bicyclic intermediate **6** was revealed from the beginning of the reaction. The moderate diastereoselection observed with 1,4-diiodobutane could be in agreement with the smaller steric hindrance of this electrophile rendering it unable to strongly discriminate between the diastereotopic faces of the lithium-enolate, i.e. the electrophile can approach both the *re* and *si* faces of **8a** and **8b**, respectively.

3. Stereochemical assignments

The configurations of the introduced stereocenters of **2** and **3** relative to the phenethyl moieties were assigned through the ^{1}H NMR chemical shifts following the methodology already employed,[1,4] the absolute configuration following on from the known (*S*)-configuration of the phenethyl groups. This approach is based on the shielding induced by the phenyl ring of the (*S*)-phenethyl group on the bridged chain protons. From a preliminary conformational analysis conducted on the simple model compound (1*S*,4*S*)-2,5-*N*,*N*-dimethyl-3,6-dioxo-2,5-diazabicyclo[2,2,4]decane **9**, conformers **9a** and **9b** have been found, the former being 7 kcal/mol more stable than the latter. Thus, on the basis of the preferred geometry **9a**, a complete conformational search of both **2** and **3** was performed showing that, as observed for analogous derivatives,[4] the conformation where the benzylic hydrogen of the (*S*)-phenethyl group is synperiplanar to the adjacent carbonyl group (the heterocyclic ring being in the boat conformation) is energetically preferred.

9a   **9b**

Since the preferred geometry for these compounds is also the doubly synperiplanar conformation,[4] the (*R*)-configuration of the two introduced stereocenters in **2** was established on the basis of the remarkable upfield shift shown by the protons of the bridged chain (which resonate at 0.6–1.65 ppm) with respect to **3** (which resonate at 1.2–2.2 ppm), according to that observed for previously investigated[4] analogous intermediates.

2   **3**

Nevertheless, the assigned configuration of the new stereocenters was unequivocally confirmed by converting the bicyclic intermediates into the corresponding α,α′-2,7-diaminosuberic acids (*R*,*R*)-**4** and (*S*,*S*)-**5** (Scheme 1). The values of $[\alpha]_D$ measured for **4**, −40.8 (*c* 0.3, 5N HCl) or −24.5 (*c* 0.22, H_2O), and for **5**, +41 (*c* 0.29, 5N HCl) or +24.6 (*c* 0.2, H_2O), are in agreement with those reported in the literature.[6a,b] Because only the diastereomer (1*S*,10*S*)-**6** was obtained, its configuration was established on the basis of the good agreement of specific rotation value $[\alpha]_D = +22.9$ (*c* 0.8, 5N HCl), measured for (*S*,*S*)-**7**, with that reported in the literature.[7]

4. Experimental

4.1. General information

^{1}H and ^{13}C NMR spectra were run on a Varian Gemini 300 spectrometer and coupling constants (J) are in hertz. Optical rotation values were measured at 25°C using a Perkin–Elmer 343 polarimeter. The reactions involving organometallic reagents were carried out under an argon atmosphere in dry solvent.

4.2. Conversion of **1** into **2** and **3**

To 1.6 g (5 mmol) of **1**, dissolved in dry THF (100 mL) at −10°C, 5.5 mmol of Na-bis(trimethylsilyl)amide base were added and the solution was stirred for 1 hour. Then the reaction mixture was cooled at −78°C and 5 mmol of 1,4-diiodobutane were added. After 1 hour, 5.5 mmol of base were added and the reaction was then slowly allowed to warm up to room temperature under stirring. Diluted HCl was then added, the mixture extracted with ethyl acetate and the organic solution evaporated in vacuo. The residue was submitted to silica gel chromatography eluting with hexane/ethyl acetate and the diastereomers **2** and **3** were separated.

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

Compound **2** was isolated pure in 52% yield. ^{1}H NMR δ ($CDCl_3$): 0.6–0.95 (m, 4H), 1.1–1.3 (m, 2H), 1.45–1.65 (m, 2H), 1.56 (d, 6H, $J=6.8$), 4.15 (dd, 2H, $J=1.6$, 7), 5.93 (q, 2H, $J=6.8$), 7.2–7.5 (m, 10ArH). ^{13}C NMR δ ($CDCl_3$): 16, 22.6, 34.4, 50.9, 56.2, 128, 128.2, 128.5, 139, 169.3; $[\alpha]_D$ −347.3 (c 0.67, $CHCl_3$). Anal. calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.5. Found: C, 76.85; H, 7.52.

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

Compound **3** was isolated pure in 28% yield. ^{1}H NMR δ ($CDCl_3$): 1.2–1.4 (m, 2H), 1.58 (d, 6H, $J=7.2$), 1.8–1.95 (m, 2H), 2–2.2 (m, 4H), 3.94 (dd, 2H, $J=2$, 6.5), 5.85 (q, 2H, $J=7.2$), 7.2–7.45 (m, 10ArH). ^{13}C NMR δ ($CDCl_3$): 16.7, 22.9, 36.1, 51.2, 56.2, 126.9, 127.9, 128.7, 139.2, 169.7; $[\alpha]_D$ −136.5 (c 0.66, $CHCl_3$). Anal. calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.5. Found: C, 76.36; H, 7.47.

4.5. (1S,10S,1′S)-11,13-Bis-[N,N-(1′-phenethyl)]-11,13-diazatricyclo[8.2.2.0^{3,8}]tetradeca-3,5,7-triene-12,14-dione **6**

Compound **6** was isolated pure in 90% yield by starting from α,α′-dibromo-o-xylene and Li-bis(trimethylsilyl)amide and following the procedure described for **2** and **3**. ^{1}H NMR δ ($CDCl_3$): 1.41 (d, 6H, $J=7.2$), 3.2 (dd, 2H, $J=6.6$, 15.3), 3.46 (dd, 2H, $J=6.6$, 15.3), 4.15 (t, 2H, $J=6.6$), 5.6 (q, 2H, $J=7.2$), 7.1–7.4 (m, 14ArH). ^{13}C NMR δ ($CDCl_3$): 16.8, 40.9, 50.4, 54.4, 126.7, 127.7, 127.9, 128.7, 131.5, 136.3, 139.9, 168.7; $[\alpha]_D$ −119.5 (c 0.66, $CHCl_3$). Anal. calcd for $C_{28}H_{28}N_2O_2$: C, 79.22; H, 6.65. Found: C, 79.51; H, 6.68.

Acknowledgements

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