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Stereocontrolled synthesis of enantiomerically pure unsaturated analogues of 2,6-DAP. Part 5☆

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Abstract—An efficient new stereocontrolled synthesis of (2*R*,6*R*)-(+)- and (2*S*,6*S*)-(−)-2,6-diamino-4-methylene-1,7-heptanedioic acid **8a** and **9a**, respectively, has been accomplished starting from the glycine-derived chiral synthon **1**. The enantiomerically pure α-alkyl derivatives **8b–d** and **9b–d** have also been synthesized. The absolute configuration of the new stereocenters was assigned on the basis of ^{1}H NMR spectra.

1. Introduction

In continuation of our program aimed at the stereospecific synthesis of novel analogues of 2,6-diaminopimelic acid (2,6-DAP),[1–4] we have recently focused our attention on both the enantiomers of the 2,6-diamino-4-methylene-1,7-heptanedioic acid (**8a**,**9a**). Our interest in this γ-methylene derivative of 2,6-DAP arises from a preliminary study by Girodeau et al.,[5] who found that it displays potent bacterial growth inhibition (*E. coli* ATCC9637), although it is a weak inhibitor of the *meso*-2,6-DAP decarboxylase which produces L-lysine. In fact, the 2,6-diamino-4-methylene-1,7-heptanedioic acid can be considered a structural variant i.e. an analog of 2,6-DAP, which is a building block of the peptidoglycan synthesized by Gram(+) and many Gram(−) bacteria. Nevertheless, it is known that the *meso*-2,6-DAP is generally a component of the peptidoglycan[6] and L-lysine is also introduced as part of the cross-linking moiety in this network, which gives rigidity to the cell wall in many bacteria. Therefore, compounds able to inhibit *meso*-2,6-DAP formation or metabolism by bacteria will possess antibiotic properties.[7]

The γ-methylene analogue of 2,6-DAP was synthesized in racemic form by means of a laborious procedure, the two enantiomers (2*S*,6*S* and 2*R*,6*R*) were then separated and the specific rotation values determined. Nevertheless, the absolute configuration of the enantiomers was not assigned.[5] On the basis of the bacteriological and enzymatic tests, performed on both isomers, Girodeau et al.[5] suggested that the target enzyme in the inhibition of L-lysine biosynthetic pathway could be L,L-DAP epimerase. However, this hypothesis was successively questioned by Vederas et al.[7] who synthesized and tested some analogues of 2,6-DAP for inhibition of *meso*-diaminopimelate D-dehydrogenase (from *B. sphaericus*) and L,L-diaminopimelate epimerase (from *E. coli*).

Herein, we describe an efficient enantioselective synthesis of (2*R*,6*R*)-**8a** and (2*S*,6*S*)-**9a** in addition to some alkyl derivatives of γ-methylene-2,6-DAP (**8b–d**, **9b–d**) which could exhibit biological activity. The synthesis of these compounds has been accomplished starting from the useful glycine derived chiral synthon **1**, already employed by us in the past in several stereocontrolled synthesis of DAP derivatives.[1–4]

2. Results and discussion

Both enantiomers of γ-methylene-2,6-DAP **8a** and **9a** have been synthesized following the efficient strategy reported in Scheme 1 and already employed by us for similar compounds, such as 2,6-diaminopimelic and 2,7-diaminosuberic acids.[1–4] The chiral synthon (*S*,*S*)-**1**,[8] submitted to alkylation with 2-chloromethyl-3-chloropropene employing 2 equiv. of base, furnished (3*R*,6*R*,1′*S*)-**2** and (3*S*,6*S*,1′*S*)-**3** in very good chemical yield with a diastereomeric ratio of 30:70 respectively.

☆ Refs. 1, 2, 3 and 4 are considered to be Parts 1, 2, 3 and 4, respectively.

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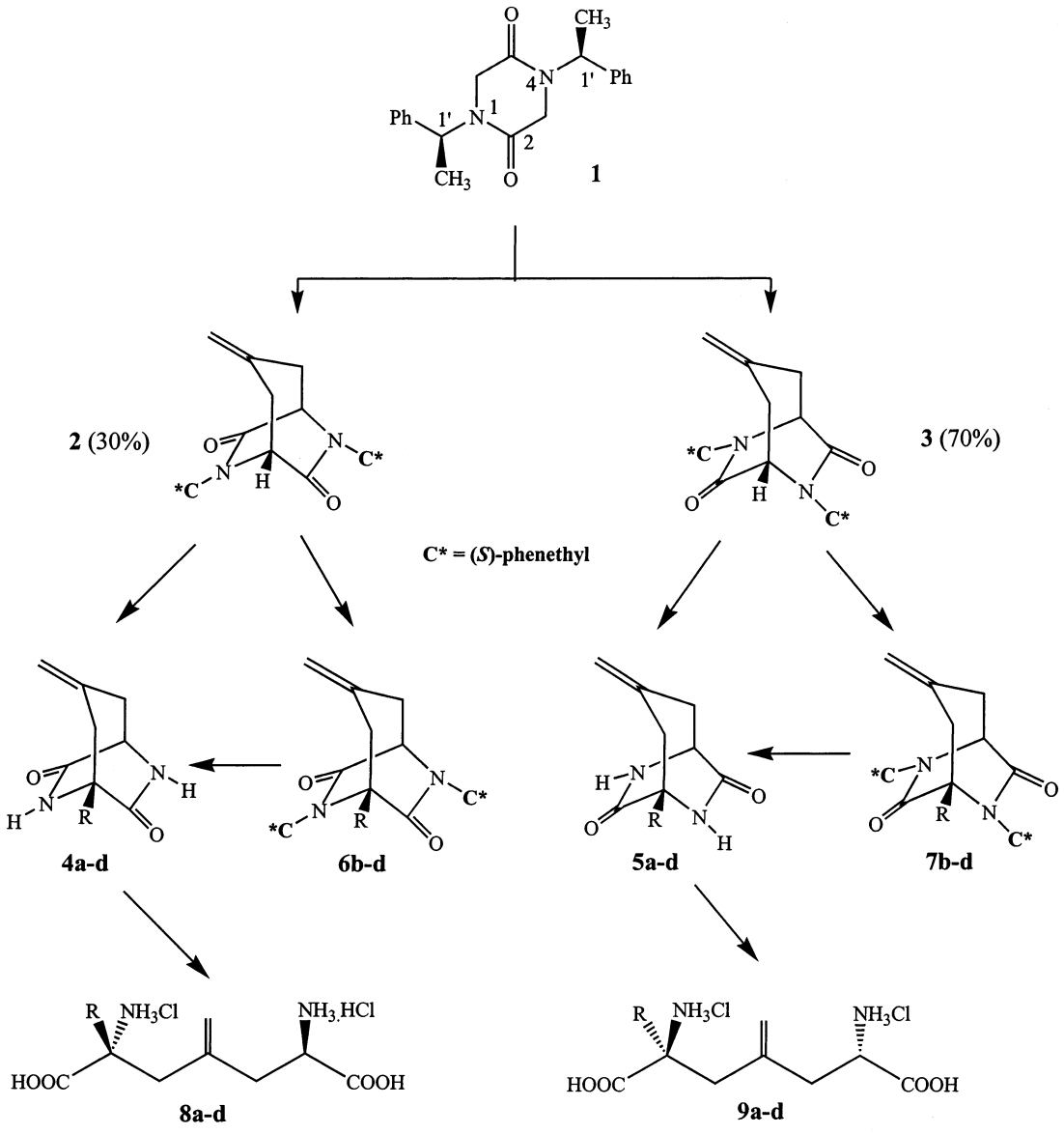
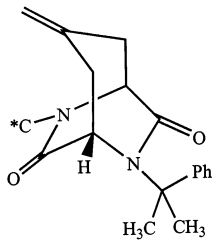


Scheme 1.

The bicyclic diastereomers, easily separable by silica gel chromatography, were submitted to the Birch reduction (Na/NH_3) to remove the chiral inductor (*S*)-phenethyl group. The intermediate enantiomers (3*R*,6*R*)-**4a** and (3*S*,6*S*)-**5a** were then obtained and subsequently furnished the optically active γ-methylene derivatives of 2,6-DAP **8a** and **9a** after hydrolysis in 2N aqueous HCl at 60°C (Scheme 1). The specific rotations determined (+20.1 (*c* 0.73, H_2O) for (2*R*,6*R*)-**8a** and −20 (*c* 0.65, H_2O) for (2*S*,6*S*)-**9a**) are higher than the values reported in the literature,[5] i.e. −18 (*c* 0.2, H_2O) and +14 (*c* 0.17, H_2O), respectively.

According to observations with a similar substrate,[3] the alkylation of **2** occurred exclusively at the bridgehead position giving the bicyclic diastereomer **6** in satisfactory to good yields and unreacted starting material (Scheme 1). In the case of diastereomer **3**, by using CH_3Li as base, the alkylation generally occurred in good yields at the bridgehead position, giving **7**. If the alkylation with CH_3I is accomplished using the bulkier n-C_4H_9Li as base, the bicyclic diastereomer **7** was formed in lower yield owing to competitive reaction at the benzylic position, which furnishes the by-products **10** and **11** (Fig. 1 and entry 8 in Table 1). Therefore, while the formation of **6** appears to be accomplished irrespective of the bulkiness of the base used, CH_3Li, which is less bulky than n-C_4H_9Li, seems to allow better yields of **7**.

It is interesting to note that it is possible to achieve good regioselectivity for the alkylation at the bridge-



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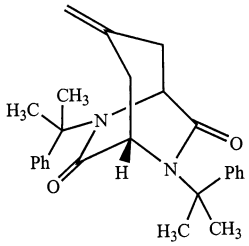

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Figure 1.

head in the bicyclic derivatives with a C4 bridge[4] or a C3 bridge with an exocyclic double bond, while in the case of the bicyclic derivative with a saturated C3 bridge[3] the regioselectivity at the bridgehead position can be accomplished only with the (3*R*,6*R*) stereoisomer. In fact, the alkylation at the bridgehead position on (3*S*,6*S*,1′*S*)-**3** and on the configurationally identical bicyclic compound with a C4 bridge[4] occurs in better yield (i.e. is more selective) in comparison with the analogous isomer with a saturated C3 bridge previously investigated.[3]

It is our opinion that the different regioselectivity generally observed between diastereomeric (3*S*,6*S*,1′*S*) and (3*R*,6*R*,1′*S*) bicyclic derivatives can be ascribed to steric factors, the competitive alkylation at the bridgehead or at the benzylic position appearing sensible to the bulkiness of the base used.[3,4] In fact, from molecular modeling studies it is possible to observe that the hydrogen at the bridgehead position is sterically more accessible in the (3*R*,6*R*,1′*S*)-isomers than in the (3*S*,6*S*,1′*S*)-isomers. Such a condition is demonstrated by the optimized geometries[9] of (3*R*,6*R*,1′*S*)-**2** and (3*S*,6*S*,1′*S*)-**3** reported in Fig. 2. Very similar geometries have also been obtained for the other bicyclic compounds previously investigated.[3,4] Therefore, the reaction at benzylic position is most probably favored for the (3*S*,6*S*,1′*S*)-isomers, especially when a bulky base is employed, because of the poorer accessibility of the bridgehead hydrogen than the benzylic one. Really, in the (3*S*,6*S*,1′*S*)-isomers the bridgehead position appears buried more deeply inside the molecule than the benzylic one (regardless of the bridge length). Among the bicyclic compounds investigated,[3,4] such an effect is more evident for the bicyclic derivative with a saturated C3 bridge.

(3*R*,6*R*,1′*S*)-**2** (3*S*,6*S*,1′*S*)-**3**

Figure 2. Optimized geometries[9] of **2** and **3**: the green ball indicates the benzylic hydrogen and the yellow ball indicates the bridgehead hydrogen.

The configuration of the new stereocenters introduced on diastereomers (3*R*,6*R*,1′*S*)-**2** and (3*S*,6*S*,1′*S*)-**3** relative to the phenethyl moiety bound to the nitrogen, has been assigned through the ^{1}H NMR chemical shifts on the basis of the methodology already employed,[1,2] the absolute configuration following on from the note (*S*)-configuration of the phenethyl group. The approach is based on the comparison between the ^{1}H NMR spectra of diastereomers **2** and **3**. In fact, owing to the thermodynamically preferred doubly *synperiplanar* conformation[2] (see Fig. 2), the bridge chain protons of (3*R*,6*R*,1′*S*)-**2** are more shielded by the phenyl ring of the (*S*)-phenethyl moiety with respect to the same protons in (3*S*,6*S*,1′*S*)-**3**. In contrast the bridgehead proton is more heavily shielded in **3** compared to **2** (see Fig. 2). The (*R*)-configuration of the two new stereocenters in **2** was established on the basis of the marked upfield shift of the CH_2 protons of the bridge chain (which resonate at 1.39 and 2.17 ppm) with respect to **3** (where they resonate at 2.5 and 2.75 ppm), according to that previously observed for analogous intermediates.[1,2] In all cases, as a consequence of the thermodynamically preferred doubly *synperiplanar* conformation, the bridgehead proton in the diastereomer **3** is less shielded (3.86 ppm) than the same proton in **2** (3.92 ppm) (Fig. 2).

Table 1. Alkylation of substrates (3*R*,6*R*,1′*S*)-**2** and (3*S*,6*S*,1′*S*)-**3**

Entry	Substrate	Base (1.3 equiv.)	R-X (1.3 equiv.)	% yield **6**	% yield **7**
1	**2**	*n*-C_4H_9Li	CH_3I	82	
2	**2**	*n*-C_4H_9Li	CH_2CHCH_2Br	70	
3	**2**	*n*-C_4H_9Li	CH_3OCH_2Br	70	
4	**2**	CH_3Li	CH_3I	85	
5	**3**	CH_3Li	CH_3I		90 (a)
6	**3**	CH_3Li	CH_2CHCH_2Br		76 (b)
7	**3**	CH_3Li	CH_3OCH_2Br		86 (c)
8	**3**	*n*-C_4H_9Li	CH_3I		77 (d)

(a) The methyl derivative **10** was obtained in 10% yield. Monoalkylation at the benzylic position was observed in 14% yield (b) and 10% yield (c); (d) the products **10** and **11** were isolated in 4 and 17% yield, respectively.

3. Experimental

3.1. General information

^{1}H 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. The coupling constants (J) are in Hz. Optical rotation values were measured at 25°C on a Perkin–Elmer 343 polarimeter. Dry THF was distilled from sodium benzophenone ketyl. Chromatographic separations were performed with silica gel 60 (230–400 mesh).

3.2. Conversion of 1 into 2 and 3

Under an inert atmosphere, to a stirred solution of **1** (9.45 g, 29.35 mmol) in dry THF (100 mL) cooled at −10°C, was added 1 M solution of LHMDS in dry THF (29.35 mL). After 30 min the reaction mixture was cooled to −78°C and then 2-chloromethyl-3-chloropropene (3.67 g, 29.35 mmol) was dropped. After about 4 h, LHMDS (1 M, 29.35 mL) was added and the mixture was then allowed to warm up to rt under stirring. Diluted aqueous HCl and ethyl acetate were added and after separation the organic solution was evaporated in vacuo. The residue was submitted to silica gel chromatography eluting with hexane/ethyl acetate and the diastereomers (**2** and **3**) were separated.

3.2.1. (3*R*,6*R*,1′*S*)-1,4-Bis-(1′-phenethyl)-2,5-dioxo-8-methylene-1,4-diazabicyclo[3.2.2]nonane, 2. The product was isolated in pure form, as an oil, in 27% yield. ^{1}H NMR δ: 1.39 (dd, 2H, J=4.5, 15); 1.52 (d, 6H, J=6.9); 2.17 (dd, 2H, J=3, 15); 3.92 (dd, 2H, J=3, 4.5); 4.45 (s, 2H); 5.79 (q, 2H, J=6.9); 7.2–7.45 (m, 10ArH). ^{13}C NMR δ: 16.2, 35.6, 50.4, 54.7, 118.6, 128.0, 128.2, 128.4, 138.3, 138.4, 168.6. $[\alpha]_D$ −243.0 (c 1.02, $CHCl_3$). Anal. calcd for $C_{24}H_{26}N_2O_2$: C, 76.98; H, 7.0; N, 7.48. Found: C, 77.27; H, 7.02; N, 7.5%.

3.2.2. (3*S*,6*S*,1′*S*)-1,4-Bis-(1′-phenethyl)-2,5-dioxo-8-methylene-1,4-diazabicyclo[3.2.2]nonane, 3. The product was isolated pure, as an oil, in 63% yield. ^{1}H NMR δ: 1.53 (d, 6H, J=7); 2.5 (dd, 2H, J=4.8, 15); 2.75 (dd, 2H, J=3.3, 15); 3.86 (dd, 2H, J=3.3, 4.8); 4.97 (s, 2H); 5.71 (q, 2H, J=7); 7.1–7.4 (m, 10ArH). ^{13}C NMR δ: 16.2, 37.3, 49.9, 54.6, 118.5, 126.3, 127.6, 128.4, 138.7, 139.3, 168.1. $[\alpha]_D$ −165.9 (c 1, $CHCl_3$). Anal. calcd for $C_{24}H_{26}N_2O_2$: C, 76.98; H, 7.0; N, 7.48. Found: C, 77.15; H, 7.01; N, 7.51%.

3.3. Conversion of 2 and 3 into 4a and 5a respectively

Under an inert atmosphere, a solution of **2** or **3** (1 mmol) in dry THF (10 mL) and t-butanol (1 mL) was added to a stirred solution of Li (0.1 g, 15 mmol) in about 50 mL of liquid ammonia cooled to −60°C. After 5 min the reaction was quenched with NH_4Cl (0.75 g) and the cooling bath was removed allowing the complete evaporation of NH_3. The crude reaction product was evaporated in vacuo and the residue submitted to silica gel chromatographic elution with ethyl acetate/methanol. Since traces of LiCl were always present, the enantiomers **4a** and **5a** were not isolated in sufficiently pure form for elemental analysis and to measure the specific rotation.

3.3.1. (3*R*,6*R*)-2,5-Dioxo-8-methylene-1,4-diazabicyclo[3.2.2]nonane, 4a. The product was isolated in about 90% yield. ^{1}H NMR (D_2O) δ: 2.5–2.8 (m, 4H); 3.88 (dd, 2H, J=3.8, 4.4); 5.03 (m, 2H). ^{13}C NMR (CD_3OD) δ: 38.3, 55.4, 119.5, 141.2, 174.2.

3.4. Conversion of 4a and 5a into 8a and 9a, respectively

A mixture of **4a** or **5a** (0.133 g, 0.8 mmol) in aqueous 2N aqueous HCl (4 mL) was stirred at 60°C and after about 40 h the solution was evaporated to dryness in vacuo. The crude reaction product was purified by adsorption on Amberlist H-15 ion exchange resin and recovered pure after elution with aqueous 5 M NH_4OH. The aqueous solution was evaporated in vacuo and the residue dissolved in aqueous 2N HCl. The acid solution was then evaporated under vacuum to dryness and the diaminodiacid **8a** or **9a** was recovered, as the hydrochloride salt, in practically quantitative yield. The enantiomeric purity of **8a** and **9a** was ascertained on the corresponding amino acids in zwitterionic form by TLC on cellulose plates, as reported in Ref. 5.

3.4.1. (2*R*,6*R*)-2,6-Diamino-4-methylene-1,7-heptanedioic acid dihydrochloride, 8a. ^{1}H NMR (D_2O) δ: 2.53 (dd, 2H, J=9.6, 15); 2.77 (dd, 2H, J=4.8, 15); 4.13 (dd, 2H, J=4.8, 9.6); 5.19 (s, 2H). ^{13}C NMR (D_2O) δ: 36.0, 51.6, 122.8, 136.0, 171.7. $[\alpha]_D$ +20.1 (c 0.73, H_2O); mp 240–2°C, with decomposition. Anal. calcd for $C_8H_{16}Cl_2N_2O_4$: C, 34.92; H, 5.86; Cl, 25.77; N, 10.18. Found: C, 35.05; H, 5.88; Cl, 25.85; N, 10.20%.

3.4.2. (2*S*,6*S*)-2,6-Diamino-4-methylene-1,7-heptanedioic acid dihydrochloride, 9a. $[\alpha]_D$ −20 (c 0.65, H_2O). Anal. calcd for $C_8H_{16}Cl_2N_2O_4$: C, 34.92; H, 5.86; Cl, 25.77; N, 10.18. Found: C, 35.0; H, 5.85; Cl, 25.82; N, 10.16%.

3.5. Alkylation of 2 and 3

Under an inert atmosphere, to a stirred solution of **2** or **3** (0.8 g, 2.14 mmol) in dry THF (20 mL) cooled at −78°C, was added n-C_4H_9Li or CH_3Li (see Table 1). After about 5 min the appropriate alkylating reagent, reported in 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 rt. Diluted 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.

3.5.1. (3*R*,6*R*,1′*S*)-1,4-Bis-(1′-phenethyl)-2,5-dioxo-3-methyl-8-methylene-1,4-diazabicyclo[3.2.2]nonane, 6b. The product was obtained, as an oil, in 85% yield by alkylating **2** with iodomethane. ^{1}H NMR δ: 1.45 (dd,

1H, $J=4.8$, 15); 1.5 (d, 3H, $J=7$); 1.68 (s, 3H); 1.78 (d, 3H, $J=7$); 2.26 (dd, 1H, $J=3.4$, 15); 2.48 (m, 2H); 3.85 (dd, 1H, $J=3.4$, 4.8); 4.60 (s, 1H); 4.8 (s, 1H); 4.9–5.3 (broad, 1H); 5.91 (q, 1H, $J=7$); 7.18–7.43 (m, 10ArH). ^{13}C NMR δ: 16.0, 18.0, 22.7, 29.5, 35.5, 46.0, 51.0, 52.6, 54.6, 63.2, 118.2, 125.8, 126.5, 127.9, 128.3, 138.3, 139.5, 141.4, 169.4, 169.6. $[\alpha]_D$ −89.7 (*c* 1.46, $CHCl_3$). Anal. calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.26; N, 7.21. Found: C, 77.55; H, 7.28; N, 7.23%.

3.5.2. (3*S*,6*R*,1′*S*)-1,4-Bis-(1′-phenethyl)-3-allyl-2,5-dioxo-8-methylene-1,4-diazabicyclo[3.2.2]nonane, 6c. The product was obtained, as an oil, in 70% yield by alkylating **2** with allylbromide. ^{1}H NMR δ: 1.54 (d, 3H, $J=7$); 1.79 (d, 3H, $J=6.8$); 2.25 (dd, 1H, $J=3.2$, 15); 2.58 (m, 3H); 2.95 (dd, 1H, $J=7$, 15.4); 3.11 (dd, 1H, $J=6$, 15.8); 3.82 (dd, 1H, $J=3.6$, 4.4); 4.61 (s, 1H); 4.88 (s, 1H); 5 (m, 1H); 5.15 (m, 1H); 5.6 (m, 1H); 5.98 (q, 1H, $J=7$); 6.0 (m, 1H); 7.3 (m, 10ArH).^{13}C NMR δ: 16.1, 17.5, 35.7, 40.2, 44.8, 50.9, 52.9, 54.4, 65.2, 118.5, 119, 125.4, 126.1, 127.5, 127.7, 127.9, 128.3, 133.1, 138.3, 139.2, 141.6, 168.7, 169.9. $[\alpha]_D$ −117.1 (*c* 1.1, $CHCl_3$). Anal. calcd for $C_{27}H_{30}N_2O_2$: C, 78.23; H, 7.29; N, 6.76. Found: C, 78.45; H, 7.3; N, 6.78%.

3.5.3. (3*S*,6*R*,1′*S*)-1,4-Bis-(1′-phenethyl)-2,5-dioxo-8-methylene-3-methoxymethyl-1,4-diazabicyclo[3.2.2]nonane, 6d. The product was obtained as an oil in 70% yield by alkylating **2** with methoxymethylbromide. ^{1}H NMR δ: 1.4–1.55 (m, 1H), 1.49 (d, 3H, $J=7$); 1.8 (d, 3H, $J=7$); 2.23 (dd, 1H, $J=3$, 14.6); 2.6 (q_{AB}, 2H, $J=15$); 3.40 (s, 3H); 3.75 (dd, 1H, $J=3$, 5.1); 3.9–4.18 (broad, 2H); 4.57 (s, 1H); 4.9 (m, 2H); 5.9 (q, 1H, $J=7$); 7.18–7.5 (m, 10ArH). ^{13}C NMR δ: 16.2, 17.2, 35.8, 41, 50.8, 54.1, 54.7, 59.1, 65.8, 73.3, 118.7, 125.7, 126.3, 127.9, 128.1, 128.4, 138.4, 139.0, 142.4, 168.0, 169.4. $[\alpha]_D$ −95.4 (*c* 0.75, $CHCl_3$). Anal. calcd for $C_{26}H_{30}N_2O_3$: C, 74.61; H, 7.23; N, 6.69. Found: C, 74.55; H, 7.2; N, 6.7%.

3.5.4. (3*S*,6*S*,1′*S*)-1, 4-Bis-(1′-phenethyl)-2,5-dioxo-3-methyl-8-methylene-1,4-diazabicyclo[3.2.2]nonane, 7b. The product was obtained, as an oil, in 90% yield by alkylating **3** with iodomethane. ^{1}H NMR δ: 1.35 (s, 3H); 1.56 (d, 3H, $J=7.2$); 1.71 (d, 3H, $J=7.2$); 2.45 (dd, 1H, $J=3.6$, 14.7); 2.51 (s, 2H); 2.73 (dd, 1H, $J=3.6$, 14.7); 3.92 (t, 1H, $J=3.6$); 4.86 (s, 1H); 4.91 (s, 1H); 5.7–6 (broad, 1H); 5.86 (q, 1H, $J=7.2$); 7.1–7.4 (m, 10ArH). ^{13}C NMR δ: 16.6, 17.8, 22.6, 37.6, 46.8, 51.0 (broad), 54.6, 63.1, 118.5, 126.3, 126.6, 126.8, 127.9, 128.3, 128.7, 139.7, 139.8, 142.0, 170.0, 170.2. $[\alpha]_D$ −76.6 (*c* 1.15, $CHCl_3$). Anal. calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.26; N, 7.21. Found: C, 77.5; H, 7.28; N, 7.2%.

3.5.5. (3*R*,6*S*,1′*S*)-1,4-Bis-(1′-phenethyl)-3-allyl-2,5-dioxo-8-methylene-1,4-diazabicyclo[3.2.2]nonane, 7c. The product was obtained, as an oil, in 76% yield by alkylating **3** with allylbromide. ^{1}H NMR δ: 1.59 (d, 3H, $J=7.4$); 1.79 (d, 3H, $J=6.9$); 2.43 (m, 3H); 2.55–2.85 (m, 2H); 2.95–3.2 (broad, 1H); 3.80 (t, 1H, $J=3.9$); 4.65 (s, 1H); 4.80 (s, 1H); 5.1–5.35 (m, 3H); 5.9 (q, 1H, $J=6.9$); 5.95–6.1 (m, 1H); 7.2–7.5 (m, 10ArH). ^{13}C NMR δ: 16.2, 19.4, 37, 39.9, 44.1, 50.7, 53.3 (broad), 54.4, 65.5, 117.9, 118.1, 126.1, 126.7, 127.3, 127.7, 128.3, 133.8, 138.7, 139.4, 141.6, 168.6, 170.1. $[\alpha]_D$ +50.9 (*c* 2.52, $CHCl_3$). Anal. calcd for $C_{27}H_{30}N_2O_2$: C, 78.23; H, 7.29; N, 6.76. Found: C, 78.5; H, 7.32; N, 6.75%.

3.5.6. (3*R*,6*S*,1′*S*)-1, 4-Bis-(1′-phenethyl)-2,5-dioxo-8-methylene-3-methoxymethyl-1,4-diazabicyclo[3.2.2]nonane, 7d. The product was obtained, as an oil, in 86% yield by alkylating **3** with methoxymethylbromide. ^{1}H NMR δ: 1.57 (d, 3H, $J=6.8$); 1.83 (d, 3H, $J=6.8$); 2.3–2.7 (m, 4H); 3.48 (s, 3H); 3.70 (dd, 1H, $J=4$, 4.6); 3.98 (broad, 2H); 4.84 (s, 2H); 5.10 (broad, 1H); 5.85 (q, 1H, $J=6.8$); 7.2–7.6 (m, 10ArH). ^{13}C NMR δ: 16.6, 18.5, 37.1, 41.1, 51.0, 55.3 (broad), 59.0, 66.3, 72.9, 118.4, 126.6, 126.7, 127.7, 127.8, 128.6, 139.0, 139.6, 141.7, 168.3, 169.6. $[\alpha]_D$ +20.8 ($c=0.83$, $CHCl_3$). Anal. calcd for $C_{26}H_{30}N_2O_3$: C, 74.61; H, 7.23; N, 6.69. Found: C, 74.5; H, 7.22; N, 6.66%.

3.6. Conversion of 6b–d and 7b–d into 4b–d and 5b-d, respectively

The procedure followed was that previously described to prepare **4a** and **5a** from **2** and **3**, respectively. The reaction products, recovered in practically quantitative yield, were submitted to silica gel chromatography eluting with hexane/ethyl acetate. However, the enantiomers **4b–d** and **5b–d** were not obtained in sufficiently pure form for elemental analysis and to measure the specific rotation because of the presence of LiCl traces.

3.6.1. (3*R*,6*R*)-2,5-Dioxo-3-methyl-8-methylene-1,4-diazabicyclo[3.2.2]nonane, 4b. The product was obtained as a wax in 92% yield. ^{1}H NMR (CD_3OD) δ: 1.38 (s, 3H); 2.4–2.7 (m, 4H); 3.82 (dd, 1H, $J=3.2$, 4.4); 4.96 (m, 2H). ^{13}C NMR (CD_3OD) δ: 20.5, 36.0, 44.7, 53.7, 57.0, 117.4, 139.9, 168.4, 169.5. $[\alpha]_D$ −86.0 (*c* 0.4, CH_3OH). Anal. calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 60.2; H, 6.7; N, 15.5%.

3.6.2. (3*S*,6*R*)-2,5-Dioxo-3-allyl-8-methylene-1,4-diazabicyclo[3.2.2]nonane, 4c. The product was obtained as a wax in 85% yield. ^{1}H NMR (CD_3OD) δ: 2.3–2.8 (m, 6H); 3.81 (dd, 1H, $J=3.4$, 4.8); 4.97 (s, 2H); 5.1–5.3 (m, 2H); 5.7–6 (m, 1H). ^{13}C NMR (CD_3OD) δ: 38, 40.4, 45.5, 55.3, 61, 119.3, 120.1, 133.4, 141.6, 174.2. $[\alpha]_D$ −117.2 (*c* 0.48, CH_3OH). Anal. calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.92; H, 6.87; N, 13.55%.

3.6.3. (3*S*,6*R*)-2,5-Dioxo-8-methylene-3-methoxymethyl-1,4-diazabicyclo[3.2.2]nonane, 4d. The product was obtained as a wax in 90% yield. ^{1}H NMR (CD_3 OD) δ: 2.52 (qAB, 2H, $J=14.6$); 2.53–2.73 (m, 2H); 3.42 (s, 3H); 3.52 (d, 1H, $J=9.6$); 3.72 (d, 1H, $J=9.6$); 3.85 (dd, 1H, $J=3.6$, 4.8); 5 (m, 2H). ^{13}C NMR (CD_3OD) δ: 38.1, 41.7, 55.3, 59.6, 61.3, 73.8, 119.5, 141.2, 173.5, 173.8. $[\alpha]_D$ −77.4 (*c* 0.42, CH_3OH). Anal. calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.1; H, 6.73; N, 13.35%.

3.6.4. (3*S*,6*S*)-2,5-Dioxo-3-methyl-8-methylene-1,4-diazabicyclo[3.2.2]nonane, 5b. The product was obtained as a wax in 91% yield. $[\alpha]_D$ +85.7 (*c* 0.38, CH_3OH). Anal. calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 60.1; H, 6.72; N, 15.6%.

3.6.5. (3*R*,6*S*)-2,5-Dioxo-3-allyl-8-methylene-1,4-diazabicyclo[3.2.2]nonane, 5c. The product was obtained as a wax in 86% yield. $[\alpha]_D$ +116.1 (*c* 0.5, CH_3OH). Anal. calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.15; H, 6.82; N, 13.6%.

3.6.6. (3*R*,6*S*)-2,5-Dioxo-3-methoxymethyl-8-methylene-1,4-diazabicyclo[3.2.2]nonane, 5d. The product was obtained as a wax in 90% yield. $[\alpha]_D$ +76.6 (*c* 0.4, CH_3OH). Anal. calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.23; H, 6.7; N, 13.38%.

3.7. Conversion of 4b–d and 5b–d into 8b–d and 9b–d, respectively

A mixture of **4b–d** or **5b–d** (0.8 mmol) in aqueous 2N HCl (4 mL) was heated at 80°C under stirring. After 12 h, the solution was evaporated in vacuo to dryness and the reaction product was worked up following the procedure previously described to obtain **8a** and **9a**. The products were recovered as the hydrochloride salts in practically quantitative yield.

3.7.1. (2*R*,6*R*)-2,6-Diamino-2-methyl-4-methylene-1,7-heptandioic acid dihydrochloride, 8b. ^{1}H NMR (D_2O) δ: 1.47 (s, 3H); 1.75 (dd, 1H, J=8.4, 15); 1.81 (d, 1H, J=14.7); 1.9 (dd, 1H, J=5.7, 15); 1.95 (d, 1H, J=14.7); 2.46 (dd, 1H, J=8.1, 15.9); 2.51 (d, 1H, J=15); 2.62 (dd, 1H, J=6, 15.3); 2.70 (d, 1H, J=15). ^{13}C NMR (D_2O) δ: 22.9, 37.5, 42.1, 51.8, 59.9, 123.7, 135.8, 171.8, 174.2. $[\alpha]_D$ +6.9 (*c* 0.79, 1N HCl). Anal. calcd for $C_9H_{18}Cl_2N_2O_4$: C, 37.38; H, 6.27; Cl, 24.52; N, 9.69. Found: C, 37.48; H, 6.3; Cl, 24.6; N, 9.72%.

3.7.2. (2*R*,6*R*)-2,6-Diamino-2-allyl-4-methylene-1,7-heptandioic acid dihydrochloride, 8c. ^{1}H NMR (D_2O) δ: 2.5 (m, 6H); 4.1 (dd, 1H, J=6, 8.1); 5.17 (s, 1H), 5.23 (s, 2H); 5.26 (s, 1H), 5.7 (m, 1H). ^{13}C NMR (D_2O) δ: 37.6, 41, 41.2, 51.9, 63.1, 123.4, 123.6, 129.5, 135.8, 171.9, 173.5. The product was not isolated in sufficiently pure form for elemental analysis and specific rotation determination.

3.7.3. (2*S*,6*R*)-2,6-Diamino-2-methoxymethyl-4-methylene-1,7-heptandioic acid dihydrochloride, 8d. ^{1}H NMR (D_2O) δ: 2.4–2.75 (m, 4H); 3.25 (s, 3H); 3.48 (d, 1H, J=10.6); 3.76 (d, 1H, J=10.6); 4.05 (dd, 1H, J=6.2, 8), 5.15 (s, 1H); 5.19 (s, 1H). ^{13}C NMR (D_2O) δ: 37.5, 37.7, 51.9, 59.8, 63.8, 74.3, 123.7, 135.3, 172.0, 172.5. The product was not isolated in sufficiently pure form for the elemental analysis and specific rotation determination.

3.7.4. (2*S*,6*S*)-2,6-Diamino-2-methyl-4-methylene-1,7-heptandioic acid dihydrochloride, 9b. $[\alpha]_D$ −6.5 (*c* 0.92, 1N HCl). Anal. calcd for $C_9H_{18}Cl_2N_2O_4$: C, 37.38; H, 6.27; Cl, 24.52; N, 9.69. Found: C, 37.48; H, 6.3; Cl, 24.6; N, 9.72%.

3.7.5. (2*S*,6*S*)-2,6-Diamino-2-allyl-4-methylene-1,7-heptanedioic acid dihydrochloride, 9c. The product was not isolated in sufficiently pure form for the elemental analysis/specific rotation determination.

3.7.6. (2*R*,6*S*)-2,6-Diamino-4-methylene-2-methoxymethyl-1,7-heptanedioic acid dihydrochloride, 9d. The product was not isolated in sufficiently pure form for the elemental analysis and to determine the specific rotation.

3.7.7. (3*S*,6*S*,1′*S*)-1-(1′-Phenethyl)-4-(1″-phenylisopropyl)-2, 5-dioxo-8-methylene-1, 4-diazabicyclo[3.2.2]-nonane, 10. ^{1}H NMR δ: 1.57 (d, 3H, J=7.4); 1.67 (s, 3H); 1.84 (s, 3H), 2.5 (m, 2H); 2.74 (bs, 1H); 2.81 (bs, 1H); 3.71 (t, 1H, J=4); 4.32 (dd, 1H, J=3.8, 4.8); 5 (s, 2H); 5.81 (q, 1H, J=7.4); 7.3 (m, 10ArH). ^{13}C NMR δ: 16.9, 27.2, 29.8, 37.5, 50.5, 56.6, 57.5, 59, 62.2, 118.5, 124.6, 126.5, 126.8, 127.8, 128.3, 128.6, 139.2, 139.7, 146.2, 168.4, 169. The product was not isolated in sufficiently pure form for the elemental analysis and to determine the specific rotation.

3.7.8. (3*S*,6*S*)-1,4-Bis-(1′-phenylisopropyl)-2,5-dioxo-8-methylene-1,4-diazabicyclo[3.2.2]nonane, 11. ^{1}H NMR δ: 1.65 (s, 6H); 1.87 (s, 6H); 2.55 (m, 4H); 4.14 (t, 2H, J=4); 5.02 (s, 2H); 7.3 (m, 10ArH). ^{13}C NMR δ: 22.7, 29.9, 37.5, 59, 61.8, 118.3, 124.7, 126.3, 126.6, 126.8, 128.3, 128.7, 146.4, 169.9. The product was not isolated in sufficiently pure form for the elemental analysis and to determine the specific rotation.

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