Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1181–1187

TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of bis(α-amino acid) derivatives isosteric with cysteine. Part 4[†,‡]

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Received 12 April 2002; accepted 30 May 2002

Abstract—Enantiomerically pure α-alkyl derivatives with α,α′-diaminodicarboxylic acids isosteric with cysteine **8a**,**b**,**e**, **9a**,**b**,**e** and **10a**,**b**,**e** have been synthesized starting from the glycine-derived chiral synthon (1′*S*,1″*S*)-**1**.

1. Introduction

Recently, we have directed our efforts towards the synthesis of enantiomerically pure α,α′-diaminodicarboxylic acids[1–3] and corresponding tripeptides,[4] as useful structural variants of 2,6-diaminopimelic acid (2,6-DAP) which is involved in the biosynthetic conversion of pyruvate and L-aspartate to L-lysine both in bacteria and higher plants. Thus, structural analogues of 2,6-DAP, which can function as inhibitors in the biosynthetic diaminopimelate pathway of L-lysine (DAP/lysine pathway), could display potential biological activity both as antibacterial[5] and herbicidal agents.[6] In fact, *meso*-2,6-DAP and L-lysine are constituents of the cell wall peptidoglycan of Gram(−) and many Gram(+) bacteria, respectively.[7,8]

Herein, we report a stereoselective synthesis of alkyl derivatives of 2,7-diaminosuberic acid and (*S*,*S*)-*ortho*-phenylene-bis-alanine which are cysteine isosteres, the disulfide bridge being substituted by an ethylene unit. Therefore, these bis(α-amino acid) derivatives with all-carbon C_4 bridges can act as substitutes for cysteine. As known, the disulfide unit in bioactive peptides confers conformational constraint to the structure which may be a very important factor in determining interactions between a biologically active substrate (a peptide or protein) and its receptor.[9] Thus, such structures, when included in small peptides, are of potential medicinal importance.

2. Results and discussion

The α,α′-diamino diacids derivatives **8a**,**b**,**e**, **9a**,**b**,**e** and **10a**,**b**,**e** have been synthesized starting from the glycine-derived chiral synthon **1**, already employed by us in the past.[1,2] The methodology followed is based on the conversion of chiral synthon **1** into the bicyclic derivatives (3*S*)-**2**[2] and (3*R*)-**3**,[2] in a 35:65 diastereomeric mixture easily separable by silica gel chromatography, or (3*S*)-**6**[2] which are alkylated and then submitted to acid-induced cleavage to bis(α-amino acid) derivatives, as summarized in Scheme 1.

The alkylation of bicyclic intermediates **2**, **3** and **6** to **4**, **5** and **7**, respectively (see Table 1), is complicated by the competitive acidity of the bridgehead hydrogens and the benzylic hydrogens of the (*S*)-phenylethyl group, as has been observed previously for analogous bicyclic compounds containing a C_3 bridge.[3] In fact, on forming the anion of diastereomer **3** by treatment with 1.2 equiv. of LHMDS and alkylating, using $PhCH_2Br$ as the electrophile, in addition to **5b**, a complex mixture containing the product alkylated at the benzylic position is recovered. The use of n-C_4H_9Li as the base allows **5b** to be obtained in good yield and no by-product is formed. In contrast, the same alkylation reaction of diastereomer **2** gives better results when CH_3Li is used as the base. Analogously, for the conversion of bicyclic derivative **6** into the corresponding monoalkyl derivative **7** the best results are achieved by using CH_3Li as the base. The moderate yield registered

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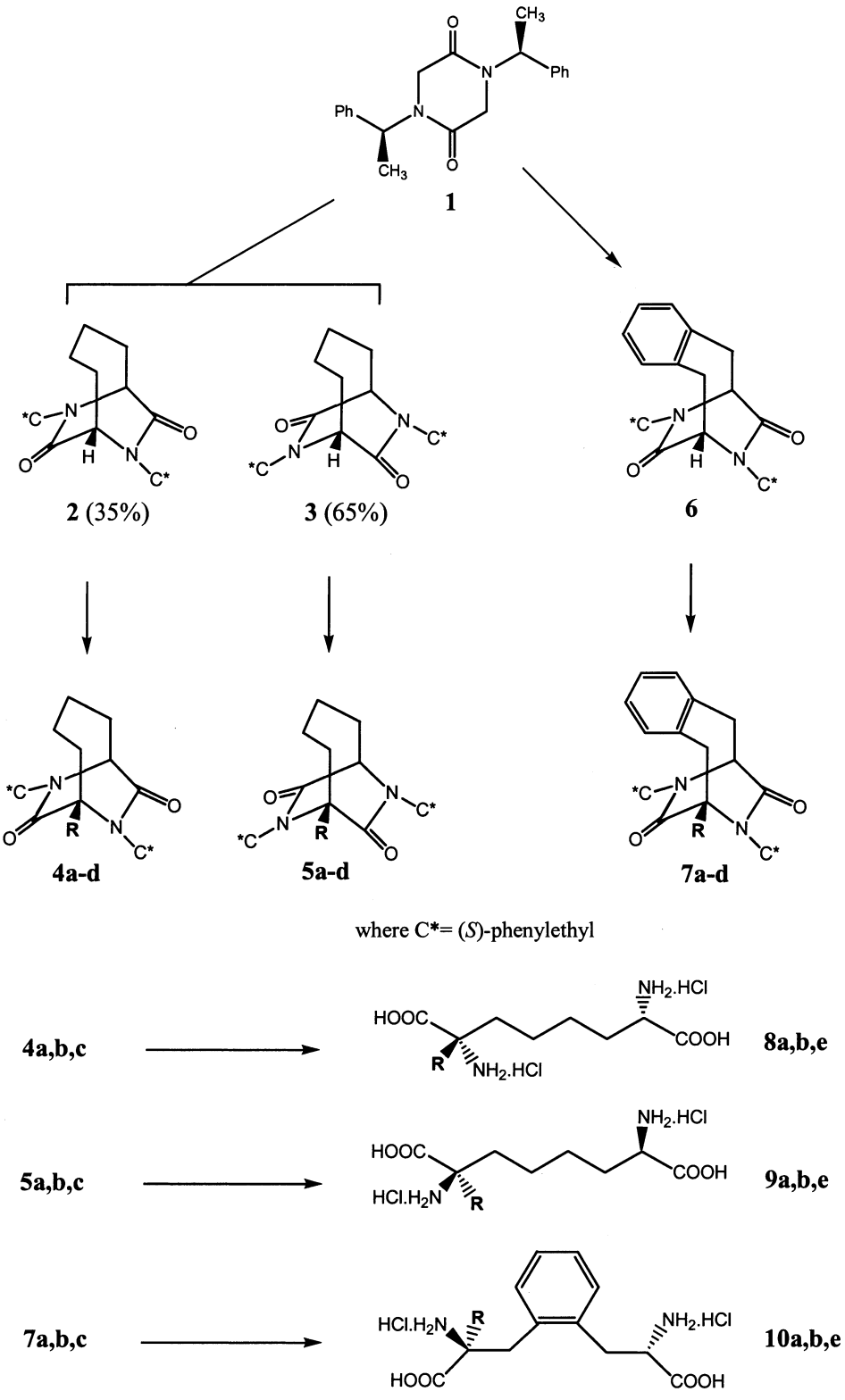
† Dedicated to Professor Gianfranco Cainelli on the occasion of his 70th birthday.

‡ For Parts 1, 2 and 3, see Refs. 1, 2 and 3, respectively.

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00262-8



Scheme 1. R = (**a**) CH_3; (**b**) CH_2Ph; (**c**) CH_2OCH_3; (**d**) CH_2CHCH_2; (**e**) CH_2OH.

when benzyl bromide is employed as electrophile (entry 10 in Table 1) is due to competitive alkylation at the benzylic position. The results collated in Table 1 clearly show that alkylation at the bridgehead position is preferred in the bicyclic derivatives with a C_4 bridge (described in this paper) compared to those with a C_3 bridge as previously reported.[3] In fact, alkylation at the bridgehead position of the (1*S*,4*S*)-diastereomer occurs in moderate yields[3] (not greater than 45%) for the bicyclic derivatives with a C_3 bridge, while good to very good yields can be obtained in the case of the corresponding bicyclic compounds carrying a C_4 bridge (Table 1). At the moment, such a difference in behaviour is not easy to explain, the factors involved probably being more than one.

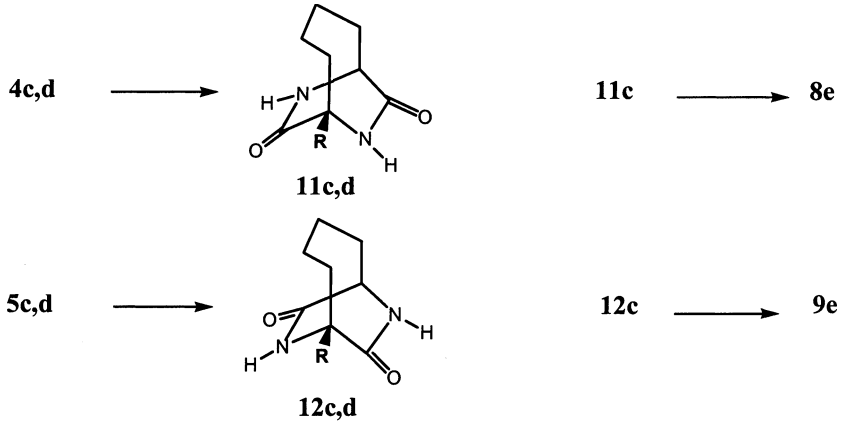
Table 1. Alkylation of (1*S*,4*S*)-**2**, (1*R*,4*R*)-**3** and (1*S*,4*S*)-**6**

Entry	Substrate	Base (equiv.)	R–X (equiv.)	Yield (%)		
				4	**5**	**7**
1	(1*S*,4*S*)-**2**	CH_3Li (1.2)	CH_3I (1.2)	93		
2	(1*S*,4*S*)-**2**	CH_3Li (1.2)	$PhCH_2Br$ (1.2)	85		
3	(1*S*,4*S*)-**2**	CH_3Li (1.2)	CH_3OCH_2Br (1.2)	92		
4	(1*S*,4*S*)-**2**	CH_3Li (1.2)	CH_2=$CHCH_2Br$ (1.2)	78		
5	(1*R*,4*R*)-**3**	*n*-C_4H_9Li (1.2)	CH_3I (1.2)		70	
6	(1*R*,4*R*)-**3**	*n*-C_4H_9Li (1.2)	$PhCH_2Br$ (1.2)		70	
7	(1*R*,4*R*)-**3**	*n*-C_4H_9Li (1.2)	CH_3OCH_2Br (1.2)		95	
8	(1*R*,4*R*)-**3**	*n*-C_4H_9Li (1.2)	CH_2=$CHCH_2Br$ (1.2)		72	
9	(1*S*,4*S*)-**6**	CH_3Li (1.3)	CH_3I (1.3)			94
10	(1*S*,4*S*)-**6**	CH_3Li (1.3)	$PhCH_2Br$ (1.3)			60[a]
11	(1*S*,4*S*)-**6**	CH_3Li (1.4)	CH_3OCH_2Br (1.2)			87
12	(1*S*,4*S*)-**6**	CH_3Li (1.3)	CH_2=$CHCH_2Br$ (1.3)			72

[a] A by-product derived from alkylation at the benzylic position has been observed.

The bicyclic intermediates **4a–c**, **5a–c** and **7a–c** were then submitted to cleavage with 57% aqueous HI[3,10] and, after adsorption on Amberlyst H-15 ion-exchange resin, the pure optically active monoalkyl derivatives of 2,7-diaminosuberic acid **8a**,**b**,**e**, **9a**,**b**,**e** and (*S*,*S*)-*ortho*-phenylene-bis-alanine **10a**,**b**,**e** can be recovered, in zwitterionic form, by eluting with 5 M aqueous ammonia. Due to the fact that hydrolysis in refluxing aqueous 57% HI is markedly slower (requiring at least 24 h) than that previously observed for analogous bicyclic compounds with a C_3 bridge,[3] the methoxymethyl group undergoes cleavage and is converted into a hydroxymethyl group. Thus, **8e**, **9e**, and **10e** are obtained from **4c**, **5c** and **7c**, respectively. Under such harsh hydrolytic conditions the double bond of the allyl group in **4d**, **5d** and **7d** also reacts and the corresponding bis(α-amino acid) derivatives cannot be isolated. To circumvent this problem, we tried a two step pathway consisting of removal of the phenylethyl group (the chiral inductor) by Birch reduction and subsequent acid hydrolysis of intermediates **11c**,**d** and **12c**,**d** (Scheme 2). Nevertheless, even using this alternative pathway, the hydrolytic conditions required (refluxing aqueous 37% HCl for at least 60 h) are drastic enough to effect cleavage of the methoxymethyl ether to a hydroxymethyl group and additionally, the allyl double bond is also reactive, giving a number of products. On the other hand, in aqueous 3N HCl hydrolysis does not occur, while in 6N HCl the reaction is very slow and after 100 h only 20% of the substrate is reacted.

Most probably, the marked decrease in the rate of acid hydrolysis observed for the bicyclic compounds **4** and **5** compared to the C_3 bridged analogues,[3] is due to the size of the intermediate lactam derived from the cleavage of one amide function. In fact, the hydrolysis of a bicyclic derivative bearing a C_3 bridge furnishes a 2-azacycleptanoic system, which is less flexible than the 2-azacyclooctanoic one derived from **4** or **5**. The greater flexibility of the eight-membered ring with respect to the seven-membered one causes a decrease in the reactivity of the lactam. The bicyclic derivatives **7**, with an *ortho*-substituted phenyl ring, showed intermediate hydrolysis rates between **4**, **5** and the bicyclic derivatives bearing a C_3 bridge.[3] In actual fact, with the same lactam ring size, the presence of the phenyl ring causes a decrease in the flexibility of the cyclic system and consequently a greater reactivity.



Scheme 2. R = (**c**) CH_2OCH_3; (**d**) CH_2CHCH_2; (**e**) CH_2OH.

3. Conclusion

In conclusion, starting from the easily prepared chiral heterocyclic synthon **1**, we have accomplished an enantioselective synthesis of 2,7-diaminodicarboxylic acid derivatives, which can be considered interesting surrogates for cysteine in biologically active small peptides. This methodology is of potential pharmacological importance due to enhanced interaction with the receptor. The approach, consisting of three steps, is simple and suitable for preparing various derivatives isosteric with cysteine.

4. Experimental

4.1. 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 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).

4.2. (1*S*,4*S*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-3,6-dioxo-2,5-diazabicyclo[4.2.2]decane 2

The procedure, NMR spectra and $[\alpha]_D$ value are reported in Ref. 2.

4.3. (1*R*,4*R*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-3,6-dioxo-2,5-diazabicyclo[4.2.2]decane 3

The procedure, NMR spectra and $[\alpha]_D$ value are reported in Ref. 2.

4.4. (1*S*,10*S*,1′*S*)-11,13-Bis-[*N*-(1′-phenethyl)]-11,13-diazatricyclo[8.2.2.0^{3,8}]tetradeca-3,5,7-triene-12,14-dione 6

The procedure, NMR spectra and $[\alpha]_D$ value are reported in Ref. 2.

4.5. Alkylation of 2, 3 and 6: general procedure

To a stirred solution of **2**, **3** or **6** (2 mmol) in dry THF (60 mL) cooled at −78°C, was added the base (see Table 1). After about 5 min the appropriate alkylating reagent 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. 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.

4.5.1. (1*S*,4*S*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-3,6-dioxo-1-methyl-2,5-diazabicyclo[4.2.2]decane 4a. Obtained by alkylating **2** with iodomethane and isolated in 93% yield. ^{1}H NMR: δ 0.9–2.2 (m, 8H), 1.4 (bs, 3H), 1.62 (d, 3H, $J=7.4$), 1.76 (d, 3H, $J=7.4$), 3.95 (d, 1H, $J=6$), 5.88 (q, 1H, $J=7.4$), 5.8–6.4 (broad, 1H), 7.2–7.5 (m, 10ArH). ^{1}H NMR (DMSO, 80°C): δ 0.88–2.24 (m, 8H), 1.37 (s, 3H), 1.58 (d, 3H, $J=7.4$), 1.7 (d, 3H, $J=7.4$), 3.82 (dd, 1H, $J=1.5$, 6), 5.69 (q, 1H, $J=7.4$), 5.71 (m, 1H), 7.15–7.35 (m, 10ArH). ^{13}C NMR: δ 16.6, 17.3, 22.7, 23.8, 25.8, 36.6, 44.9, 51 (broad), 52.2, 55.8, 65, 126.7, 126.9, 127.8, 128, 128.6, 139.2, 142.1, 171.4, 171.6. $[\alpha]_D=-49.7$ (c 0.84, $CHCl_3$). Anal. calcd for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.66; H, 7.77; N, 7.15%.

4.5.2. (1*R*,4*S*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-1-benzyl-3,6-dioxo-2,5-diazabicyclo[4.2.2]decane 4b. Obtained by alkylating **2** with benzyl bromide and isolated in 85% yield. ^{1}H NMR: δ 0.44–2.27 (m, 8H), 1.27 (d, 3H, $J=7$), 1.66 (d, 3H, $J=7.3$), 3.21 (d, 1H, $J=16.8$), 3.93 (dd, 1H, $J=1.4$, 6.6), 4.43 (q, 1H, $J=7$), 4.48 (d, 1H, $J=16.8$), 5.79 (q, 1H, $J=7.3$), 7–7.8 (m, 15ArH). ^{13}C NMR: δ 17.1, 20.8, 22, 23.1, 37.3, 43.8, 44.1, 53.9, 56.7, 58.2, 69.7, 126.4, 127.6, 128.1, 128.3, 128.6, 128.9, 129.4, 136.5, 139.1, 141.9, 170.7, 170.8. $[\alpha]_D=+94.8$ (c 0.22, $CHCl_3$). Anal. calcd for $C_{31}H_{34}N_2O_2$: C, 79.79; H, 7.34; N, 6. Found: C, 80.02; H, 7.36; N, 5.98%.

4.5.3. (1*R*,4*S*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-3,6-dioxo-1-methoxymethyl-2,5-diazabicyclo[4.2.2] decane 4c. Obtained by alkylating **2** with bromomethyl methyl ether and isolated in 92% yield. ^{1}H NMR: δ 0.65–2.13 (m, 8H), 1.61 (d, 3H, $J=7.2$), 1.89 (d, 3H, $J=6.9$), 3.38 (s, 3H), 3.69 (dd, 1H, $J=1.8$, 6.6), 3.83 (d, 1H, $J=10.2$), 4.33 (d, 1H, $J=10.2$), 4.78 (q, 1H, $J=7.2$), 5.81 (q, 1H, $J=6.9$), 7.15–7.7 (m, 10ArH). ^{13}C NMR: δ 16.4, 19.5, 22.1, 22.4, 36.4, 37.7, 52.4, 56, 56.1, 58.6, 69.1, 74.3, 126.8, 126.9, 127.3, 128.3, 138.8, 141.2, 169.5, 170.3. $[\alpha]_D$ 133.7 (c 1.04, $CHCl_3$). Anal. calcd for $C_{26}H_{32}N_2O_3$: C, 74.26; H, 7.67; N, 6.66. Found: C, 74.17; H, 7.7; N, 6.67%.

4.5.4. (1*R*,4*S*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-1-allyl-3,6-dioxo-2,5-diazabicyclo[4.2.2]decane 4d. Obtained by alkylating **2** with allyl bromide and isolated in 78% yield. ^{1}H NMR: δ 0.4–2.2 (m, 8H), 1.62 (d, 3H, $J=7.4$), 1.86 (d, 3H, $J=7.1$), 2.77 (dd, 1H, $J=7.6$, 15.6), 3.55 (m, 1H), 3.75 (dd, 1H, $J=1.4$, 6.4), 4.66 (q, 1H, $J=7.1$), 5.3 (m, 2H), 5.64–5.84 (m, 2H), 7.2–7.77 (m, 10ArH). ^{13}C NMR: δ 16.7, 21.3, 21.9, 22.7, 36.9, 41.9, 42.8, 53, 56.2, 56.7, 69.3, 118.3, 126.9, 127.4, 127.6, 127.9, 128.5, 129.1, 132.7, 139, 141.6, 170.2, 171.3. $[\alpha]_D=+207.1$ (c 1.26, $CHCl_3$). Anal. calcd for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 7.74; N, 6.73. Found: C, 77.59; H, 7.76; N, 6.7%.

4.5.5. (1*R*,4*R*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-3,6-dioxo-1-methyl-2,5-diazabicyclo[4.2.2]decane 5a. Obtained by alkylating **3** with iodomethane and isolated in 70% yield. ^{1}H NMR: δ 0.75–2.13 (m, 8H), 1.57 (d, 3H, $J=7.4$), 1.71 (s, 3H), 1.84 (d, 3H, $J=6.9$), 4.02 (dd, 1H, $J=1.4$, 6.8), 4.63–4.95 (broad, 1H), 5.96 (q, 1H, $J=$

7.4), 7.15–7.5 (m, 10ArH). ^{13}C NMR: δ 16.7, 18.8, 22.5, 24.6, 26.5, 35.5, 43.5, 52.1, 54.4, 56.4, 65.9, 126.4, 126.9, 128.3, 128.4, 139.7, 142.4, 170.4, 171. $[\alpha]_D = -168.2$ (c 1.41, $CHCl_3$). Anal. calcd for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 77.1; H, 7.75; N, 7.15%.

4.5.6. (1*S*,4*R*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-1-benzyl-3,6-dioxo-2,5-diazabicyclo[4.2.2]decane 5b. Obtained by alkylating **3** with benzyl bromide and isolated in 70% yield. ^{1}H NMR: δ 0.94–2.3 (m, 8H), 1.67 (d, 3H, $J=7.4$), 1.8 (d, 3H, $J=7$), 3 (d, 1H, $J=16$), 4.07 (dd, 1H, $J=1$, 6.2), 4.29 (d, 1H, $J=16$), 4.69 (q, 1H, $J=7$), 5.87 (q, 1H, $J=7.4$), 6.56–7.53 (m, 15ArH). ^{13}C NMR: δ 16.1, 17.6, 21.8, 23.7, 35.7, 43.5, 43.8, 52.7, 54.4, 56.7, 69.2, 125.2, 125.7, 125.9, 126.9, 127.7, 127.8, 128.1, 129.1, 135.6, 139.1, 140.9, 170.5, 170.7. $[\alpha]_D = -187.5$ (c 1.03, $CHCl_3$). Anal. calcd for $C_{31}H_{34}N_2O_2$: C, 79.79; H, 7.34; N, 6. Found: C, 80.08; H, 7.37; N, 6.01%.

4.5.7. (1*S*,4*R*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-3,6-dioxo-1-methoxymethyl-2,5-diazabicyclo[4.2.2] decane 5c. Obtained by alkylating **3** with bromomethyl methyl ether and isolated in 95% yield. ^{1}H NMR: δ 0.74–2.05 (m, 8H), 1.59 (d, 3H, $J=7.4$), 1.82 (d, 3H, $J=7$), 3.25 (s, 3H), 3.68 (d, 1H, $J=10.2$), 3.96 (dd, 1H, $J=1.6$, 6.6), 4.31 (d, 1H, $J=10.2$), 4.74 (q, 1H, $J=7$), 6.02 (q, 1H, $J=7.4$), 7.15–7.56 (m, 10ArH). ^{13}C NMR: δ 16, 16.6, 22, 22.6, 34.7, 37.8, 51.3, 53.3, 55.5, 58.2, 68.1, 74.1, 125.5, 125.8, 127.1, 127.4, 127.5, 127.9, 139, 141.9, 168.8, 170.1. $[\alpha]_D = -224.9$ (c 0.53, $CHCl_3$). Anal. calcd for $C_{26}H_{32}N_2O_3$: C, 74.26; H, 7.67; N, 6.66. Found: C, 74.51; H, 7.7; N, 6.64%.

4.5.8. (1*S*,4*R*,1′*S*)-2,5-Bis-[*N*-(1′-phenethyl)]-1-allyl-3,6-dioxo-2,5-diazabicyclo[4.2.2]decane 5d. Obtained by alkylating **3** with allyl bromide and isolated in 72% yield. ^{1}H NMR: δ 0.75–2.18 (m, 8H), 1.62 (d, 3H, $J=7.4$), 1.85 (d, 3H, $J=6.6$), 2.58 (dd, 1H, $J=7.4$, 15.4), 3.35 (m, 1H), 4.04 (dd, 1H, $J=1.4$, 7), 4.72 (q, 1H, $J=6.6$), 4.86–5 (m, 2H), 5.47 (m, 1H), 5.96 (q, 1H, $J=7.4$), 7.15–7.54 (m, 10ArH). ^{13}C NMR: δ 16.8, 18.3, 22, 23.7, 35.5, 42.1, 42.6, 51.8, 54.4, 56, 68.7, 118.7, 126, 126.2, 127.6, 127.8, 127.9, 128.3, 132.3, 139.1, 142.2, 170, 171.2. $[\alpha]_D = -185.4$ (c 0.58, $CHCl_3$). Anal. calcd for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 7.74; N, 6.73. Found: C, 78.11; H, 7.77; N, 6.7.

4.5.9. (1*S*,10*S*,1′*S*)-11,13-Bis-[*N*-(1′-phenethyl)]-1-methyl-11,13 - diazatricyclo[8.2.2.0^{3,8}]tetradeca - 3,5,7 - triene-12,14-dione 7a. Obtained by alkylating **6** with iodomethane and isolated in 94% yield. ^{1}H NMR: δ 1.4 (d, 3H, $J=7.2$), 1.48 (s, 3H), 1.68 (d, 3H, $J=7.8$), 3.19 (q_{AB}, 2H, $J=15.3$), 3.27 (dd, 1H, $J=7.8$, 15.5), 3.46 (dd, 1H, $J=5$, 15.5), 4.31 (dd, 1H, $J=5$, 7.8), 5.63 (q, 1H, $J=7.2$), 5.8 (m, 1H), 6.96–7.42 (m, 14ArH). ^{13}C NMR: δ 16.4, 17.5, 25.7, 39.8, 50.8 (broad), 51.7, 54, 63.4, 126.1, 126.3, 126.4, 127.1, 127.2, 127.4, 128, 128.3, 130.6, 135.7, 136.4, 140.1, 141.8, 169.8, 171.1. $[\alpha]_D = -31.4$ (c 1.57, $CHCl_3$). Anal. calcd for $C_{29}H_{30}N_2O_2$: C, 79.42; H, 6.9; N, 6.39. Found: C, 79.21; H, 6.88; N, 6.36%.

4.5.10. (1*S*,10*S*,1′*S*)-11,13-Bis-[*N*-(1′-phenethyl)]-1-benzyl-11,13-diazatricyclo[8.2.2.0^{3,8}]tetradeca-3,5,7-triene-12,14-dione 7b. Obtained by alkylating **6** with benzyl bromide and isolated in 60% yield. ^{1}H NMR: δ 1.36 (d, 3H, $J=7$), 1.38 (d, 3H, $J=7.4$), 2.91 (d, 1H, $J=15$), 3.21 (d, 1H, $J=15$), 3.31 (d, 2H, $J=6.4$), 3.43 (d, 1H, $J=16.8$), 4.4 (t, 1H, $J=6.4$), 4.46 (d, 1H, $J=16.8$), 4.59 (q, 1H, $J=7$), 5.37 (q, 1H, $J=7.4$), 6.78–7.71 (m, 19ArH). ^{13}C NMR: δ 17.6, 20.5, 40.1, 44.2, 51.1, 52.4, 54.6, 57.7, 68.4, 126.3, 126.6, 127.3, 127.5, 127.6, 128.2, 128.5, 128.6, 128.7, 128.8, 131, 131.4, 134.9, 136.6, 137.2, 141.3, 142.7, 168.3, 171.7. $[\alpha]_D = +30.7$ (c 0.91, $CHCl_3$). Anal. calcd for $C_{35}H_{34}N_2O_2$: C, 81.68; H, 6.66; N, 5.44. Found: C, 81.91; H, 6.68; N, 5.42%.

4.5.11. (1*R*,10*S*,1′*S*)-11,13-Bis-[*N*-(1′-phenethyl)]-1-methoxymethyl-11,13-diazatricyclo[8.2.2.0^{3,8}]tetradeca-3,5,7-triene-12,14-dione 7c. Obtained by alkylating **6** with bromomethyl methyl ether and the product was isolated in 87% yield. ^{1}H NMR: δ 1.29 (d, 3H, $J=7.4$), 1.82 (d, 3H, $J=7$), 2.68–3.12 (broad, 2H), 3.15–3.36 (m, 2H), 3.5 (s, 3H), 3.86–4.47 (broad, 3H), 4.7–5.2 (broad, 1H), 5.54 (q, 1H, $J=7.4$), 6.82–7.63 (m, 14ArH). ^{13}C NMR: δ 16.6, 19.4 (broad), 39.5, 45.6, 51.2, 54.4, 56.3 (broad), 59, 67.4 (broad), 73.5, 126.4, 126.9, 127.3, 127.4, 127.5, 127.9, 128.3, 128.5, 130.7, 131.3, 135.7, 136.4, 140, 142, 167.9, 171.1. $[\alpha]_D = +82.4$ (c 2.08, $CHCl_3$). Anal. calcd for $C_{30}H_{32}N_2O_3$: C, 76.9; H, 6.88; N, 5.98. Found: C, 76.8; H, 6.85; N, 6.0%.

4.5.12. (1*S*,10*S*,1′*S*)-11,13-Bis-[*N*-(1′-phenethyl)]-1-allyl-11,13 - diazatricyclo[8.2.2.0^{3,8}]tetradeca - 3,5,7 - triene-12,14-dione 7d. Obtained by alkylating **6** with allyl bromide and isolated in 72% yield. ^{1}H NMR: δ 1.29 (d, 3H, $J=7.4$), 1.79 (d, 3H, $J=7$), 2.8–3.2 (bm, 3H), 3.2–3.5 (bm, 3H), 4.18 (dd, 1H, $J=4.8$, 8.8), 5–5.2 (broad, 1H), 5.2–5.4 (m, 2H), 5.5 (q, 1H, $J=7.4$), 5.8–6.1 (m, 1H), 6.9–7.6 (m, 14ArH). ^{13}C NMR: δ 16.6, 20.1, 39.4, 42.8, 49.7, 51.1, 54.2, 55 (broad), 67, 118.4, 126.1, 127, 127.2, 127.4, 128, 128.2, 128.4, 130.4, 131.2, 134.6, 135.3, 136.8, 140.3, 142.1, 168.3, 172.1. $[\alpha]_D$ 77.2 (c 1.94, $CHCl_3$). Anal. calcd for $C_{31}H_{32}N_2O_2$: C, 80.14; H, 6.94; N, 6.03. Found: C, 80.32; H, 6.97; N, 6.01%.

4.6. Acid hydrolysis of bicyclic intermediates 4a–c, 5a–c and 7a–c: general procedure

The procedure used is described in Ref. 10. The crude reaction product was purified by adsorption on Amberlyst H-15 ion-exchange resin and recovered in pure form 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 evaporated under vacuum to dryness and the diamino diacid, as its hydrochloride, was then recovered in practically quantitative yield.

4.6.1. (2*S*,7*S*)-2-Methyl-2,7-diaminosuberic acid dihydrochloride 8a. The product was obtained by refluxing **4a** for about 24 h. ^{1}H NMR (D_2O): δ 1.09–1.4 (m, 2H),

1.4–1.62 (m, 1H), 1.42 (s, 3H), 1.63–2.08 (m, 5H), 3.88 (t, 1H, $J=6.3$). ^{13}C NMR: δ 22.4, 23.2, 24.7, 30, 36.9, 53.4, 60.7, 172.5, 174.5. $[\alpha]_D$ 31.1 (*c* 0.49, 1N HCl). Anal. calcd for $C_9H_{20}Cl_2N_2O_4$: C, 37.13; H, 6.92; N, 9.62. Found: C, 37.05; H, 6.95; N, 9.6.

4.6.2. (2*R*,7*S*)-2-Benzyl-2,7-diaminosuberic acid dihydrochloride 8b. The product was obtained by refluxing **4b** for about 24 h. ^{1}H NMR (D_2O): δ 1.05–2.04 (m, 8H), 2.86 (d, 1H, $J=14.3$), 3.18 (d, 1H, $J=14.3$), 3.58 (t, 1H, $J=6.2$), 7.04–7.33 (m, 5ArH). ^{13}C NMR: δ 23.5, 25.1, 30.7, 36.3, 42.5, 55.3, 66.3, 128.4, 129.6, 130.7, 134.5, 175.3, 175.7. $[\alpha]_D=+18.2$ (*c* 0.18, 1N HCl). Anal. calcd for $C_{14}H_{24}Cl_2N_2O_4$: C, 47.33; H, 6.81; N, 7.89. Found: C, 47.19; H, 6.83; N, 7.91%.

4.6.3. (2*R*,7*S*)-2-Hydroxymethyl-2,7-diaminosuberic acid dihydrochloride 8e. The product was obtained by refluxing **4c** for about 30 h. It can be also obtained in very good yield by refluxing **11c** for at least 60 h in 37% HCl. ^{1}H NMR (D_2O): δ 0.98–1.5 (m, 4H), 1.52–2 (m, 4H), 3.59 (d, 1H, $J=12.1$), 3.87 (d, 1H, $J=12.1$), 3.89 (m, 1H). ^{13}C NMR: δ 22.8, 24.7, 29.9, 31.9, 53.3, 64.2, 65.7, 172.4, 172.6. $[\alpha]_D=+20.9$ (*c* 0.96, 1N HCl). Anal. calcd for $C_9H_{20}Cl_2N_2O_5$: C, 35.19; H, 6.56; N, 9.12. Found: C, 35.3; H, 6.54; N, 9.1%.

4.6.4. (2*R*,7*R*)-2-Methyl-2,7-diaminosuberic acid dihydrochloride 9a. The product was obtained from **5a**. $[\alpha]_D=-31.5$ (*c* 0.53, 1N HCl).

4.6.5. (2*S*,7*R*)-2-Benzyl-2,7-diaminosuberic acid dihydrochloride 9b. The product was obtained from **5b**. $[\alpha]_D=-18.8$ (*c* 0.15, 1N HCl).

4.6.6. (2*S*,7*R*)-2-Hydroxymethyl-2,7-diaminosuberic acid dihydrochloride 9e. The product was obtained from **5c**. It can be also obtained in very good yield by refluxing **12c** for at least 60 h in 37% HCl. $[\alpha]_D=-21.4$ (*c* 0.82, 1N HCl).

4.6.7. (2′*S*,2″*S*)-1[(2′-Amino-2′-carboxy-2′-methyl)ethyl]-2-[(2″-amino-2″-carboxy)ethyl]benzene dihydrochloride 10a. The product was obtained by refluxing **7a** for about 24 h. ^{1}H NMR (D_2O): δ 1.44 (s, 3H), 3.02 (dd, 1H, $J=8$, 15), 3.13 (q_{AB}, 2H, $J=15.8$), 3.26 (dd, 1H, $J=6.6$, 15), 3.77 (dd, 1H, $J=6.6$, 8), 7.1–7.3 (m, 4ArH). ^{13}C NMR: δ 22.8, 34.2, 39.2, 56.3, 62.6, 128.6, 128.9, 131.3, 131.9, 133.8, 135.4, 174.1, 176.3. $[\alpha]_D=+5.6$ (*c* 1.26, 1N HCl). Anal. calcd for $C_{13}H_{20}Cl_2N_2O_4$: C, 46.03; H, 5.94; N, 8.26. Found: C, 46.13; H, 5.92; N, 8.24%.

4.6.8. (2′*R*,2″*S*)-1[(2′-Amino-2′-benzyl-2′-carboxy)ethyl]-2-[(2″-amino-2″-carboxy)ethyl]benzene dihydrochloride 10b. The product was obtained by refluxing **7b** for about 24 h. ^{1}H NMR (D_2O): δ 3 (d, 1H, $J=14.6$), 3.07–3.37 (m, 2H), 3.2 (d, 1H, $J=14.6$), 3.45 (d, 2H, $J=14.6$), 4.02 (t, 1H, $J=7.2$), 7.11–7.35 (m, 9ArH). ^{13}C NMR: δ 33.7, 38.4, 42, 54.9, 66.1, 128.9, 129.2, 129.6, 129.8, 130.8, 131.6, 132.2, 132.6, 133.3, 134.8, 172, 173.3. $[\alpha]_D=-10.7$ (*c* 0.51, 1N HCl). Anal. calcd for $C_{19}H_{24}Cl_2N_2O_4$: C, 54.95; H, 5.82; N, 6.75. Found: C, 55.07; H, 5.8; N, 6.76%.

4.6.9. (2′*R*,2″*S*)-1[(2′-Amino-2′-carboxy-2′-hydroxymethyl)ethyl] - 2 - [(2″ - amino - 2″ - carboxy)ethyl]benzene dihydrochloride 10e. The product was obtained by refluxing **7c** for about 30 h. ^{1}H NMR (D_2O): δ 3.02–3.32 (m, 4H), 3.7 (d, 1H, $J=12.1$), 3.98 (d, 1H, $J=12.1$), 4.06 (q, 1H, $J=6.6$, 8.4), 7.1–7.4 (m, 4ArH). ^{13}C NMR: δ 33.2, 34.4, 54.7, 63.7, 66.2, 129.2, 129.6, 131.5, 132.1, 134.5, 171.7, 172.1. $[\alpha]_D=+10.6$ (*c* 0.44, 1H HCl). Anal. calcd for $C_{13}H_{20}Cl_2N_2O_5$: C, 43.96; H, 5.68; N, 7.89. Found: C, 43.8; H, 5.7; N, 7.86%.

4.7. Conversion of 4c,d and 5c,d into 11c,d and 12c,d: general procedure

Under an inert atmosphere, a solution of **4c**,**d** or **5c**,**d** (1.5 mmol) in dry THF (10 mL) and *t*-butanol (1 mL) was added to a stirred solution of Na (0.46 g, 20 mmol) in liquid ammonia (about 60 mL) cooled to −60°C. After 5 min the reaction was quenched with NH_4Cl (1 g) and the cooling bath was removed to allow the complete evaporation of NH_3. Water was added, the crude product was extracted with ethyl acetate and the organic solvent evaporated in vacuo The product was recovered pure after silica gel chromatography eluting with hexane/ethyl acetate in very good yield.

4.7.1. (1*R*,4*S*)-3,6-Dioxo-1-methoxymethyl-2,5-diazabicyclo[4.2.2]decane 11c. The product was obtained from compound **4c**. ^{1}H NMR (CH_3OD): δ 1.38–1.66 (m, 2H), 167–1.92 (m, 4H), 1.95–2.2 (m, 2H), 3.37 (s, 3H), 3.39 (d, 1H, $J=9.6$), 3.73 (d, 1H, $J=9.6$), 3.94 (dd, 1H, $J=3$, 4.8). ^{13}C NMR: δ 23.9, 24.2, 37.2, 40.1, 56.1, 59.5, 62.8, 76.2, 173.7, 173.9. $[\alpha]_D=+164.6$ (*c* 1.15, CH_3OH). Anal. calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.08; H, 7.68; N, 8.88%.

4.7.2. (1*R*,4*S*)-1-Allyl-3,6-dioxo-2,5-diazabicyclo[4.2.2]decane 11d. The product was obtained from compound **4d**. ^{1}H NMR (CH_3OD): δ 1.43–2.28 (m, 8H), 2.21 (m, 1H), 2.75–2.86 (m, 1H), 3.91 (dd, 1H, $J=3$, 5.2), 5.05–5.26 (m, 2H), 5.62–5.85 (m, 1H). ^{13}C NMR: δ 23.8, 24.7, 37.4, 43.1, 44.8, 56.2, 71.1, 119.7, 133.6, 174, 174.5. $[\alpha]_D=+239$ (*c* 0.79, CH_3OH). Anal. calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.25; H, 7.76; N, 8.94%.

4.7.3. (1*S*,4*R*)-3,6-Dioxo-1-methoxymethyl-2,5-diazabicyclo[4.2.2]decane 12c. The product was obtained from **5c**. $[\alpha]_D=-166$ (*c* 0.73, CH_3OH).

4.7.4. (1*S*,4*R*)-1-Allyl-3,6-dioxo-2,5-diazabicyclo[4.2.2]decane 12d. The product was obtained from **5d**. $[\alpha]_D=-240.7$ (*c* 0.32, CH_3OH).

Acknowledgements

Thanks are due to MIUR (COFIN 2000) and to the University of Bologna for financial support.

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