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A facile and effective synthesis of lipophilic 2,6-diketopiperazine analogues

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ABSTRACT

Adamantane and cyclooctane lipophilic 2,6-diketopiperazines (2,6-DKPs) have been prepared by a simple and effective method, including the synthesis of the corresponding iminodiacetic amido-ester derivatives and their intramolecular cyclization. In this method, the key step of the imide formation was accomplished by a novel base-induced cyclization protocol, which involved the treatment of amido-ester 2,6-DKP precursors with potassium bis(trimethylsilyl)amide. Moreover, the cyclization methodology used allowed the synthesis of the respective 1-functionalized 2,6-DKPs in one pot and in excellent yields when the same primary amido-esters were treated with the previous base and the intermediate potassium imidate salts were then reacted with the electrophile benzyl bromoacetate. Hydrogenolysis of the benzyl 2,6-diketopiperazine acetates afforded the respective carboxylic acids, which constitute versatile intermediates in the synthesis of peptidomimetics and other bioactive molecules concerning our pharmacological studies.

1. Introduction

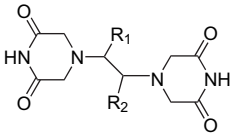
The head to head cyclic dipeptide framework of the 2,6-diketopiperazine (2,6-DKP) is present in several biologically active compounds, and it serves as an effective template for construction of conformationally constrained analogues. Among the 2,6-diketopiperazine structures, the bis(2,6-diketopiperazine) derivatives ICRF-154, ICRF-159, and ICRF-193 (Fig. 1) have been proved to be promising antitumor agents, through the inhibition of DNA topoisomerase II,[1] whereas some 1,4-disubstituted 2,6-DKP derivatives were found to display potent in vitro inhibition of leukemia and Hep cells' growth.[2] Additionally, flutimide[3] (a fungus-derived endonuclease inhibitor of influenza virus) is a structural 2,6-diketo-Δ3-piperazine motif (Fig. 1).

On the other hand, adamantane is frequently found in biologically active compounds across a number of different pharmacological activities (antiviral, antibacterial, trypanocidal, anticancer, and anti-Parkinsonic activity).[4] The cage-like structure of the adamantane, present in bioactive compounds, improves their lipophilicity.[5] Therefore, during last years the adamantane derivatives have attracted considerable attention.

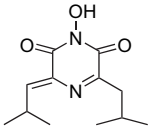
As part of our research, concerning pharmacological studies, we were interested in preparing analogues incorporating the bulky lipophilic adamantane or cyclooctane ring to the 2,6-DKP core structure. Thus, we synthesized the novel adamantane and cyclooctane spiro heterocycles **10a**,**b** and **11**, and their 1-substituted derivatives **13a**,**b**, **14**, **16a**,**b**, and **17**, as well as the 3-adamantyl-2,6-diketopiperazine derivatives **12**, **15**, and **18** (Table 1), by a new effective synthetic procedure outlined in Scheme 1. Particularly, carboxylic acids **16**–**18** appeared as useful building blocks in the preparation of our target compounds.

2. Results and discussion

The synthesis of 2,6-diketopiperazines (2,6-DKPs) by intramolecular cyclization of iminodiacetic acid derivatives (amido-esters or amido-carboxylic acids) is well established.[6] Acyclic 2,6-DKP precursors commonly contain a primary or secondary amide group, as a nucleophilic nitrogen source, and a carboxyl or ester group, as the electrophilic moiety. Several variations of the reaction conditions, depending on the nature of the iminodiacetic derivative and the demands of the 2,6-DKP ring substitution, have appeared in the literature.[2,3,6,7] In the case of amido-ester 2,6-DKP precursors, the base-catalyzed intramolecular cyclization reaction is the most preferred route in producing 2,6-DKPs.



ICRF-154 : R_1=H, R_2=H
ICRF-159 : R_1=H, R_2=CH_3
ICRF-193 : R_1=CH_3, R_2=CH_3



Flutimide

Figure 1. Structures of ICRF-154, ICRF-159, ICRF-193, and flutimide.

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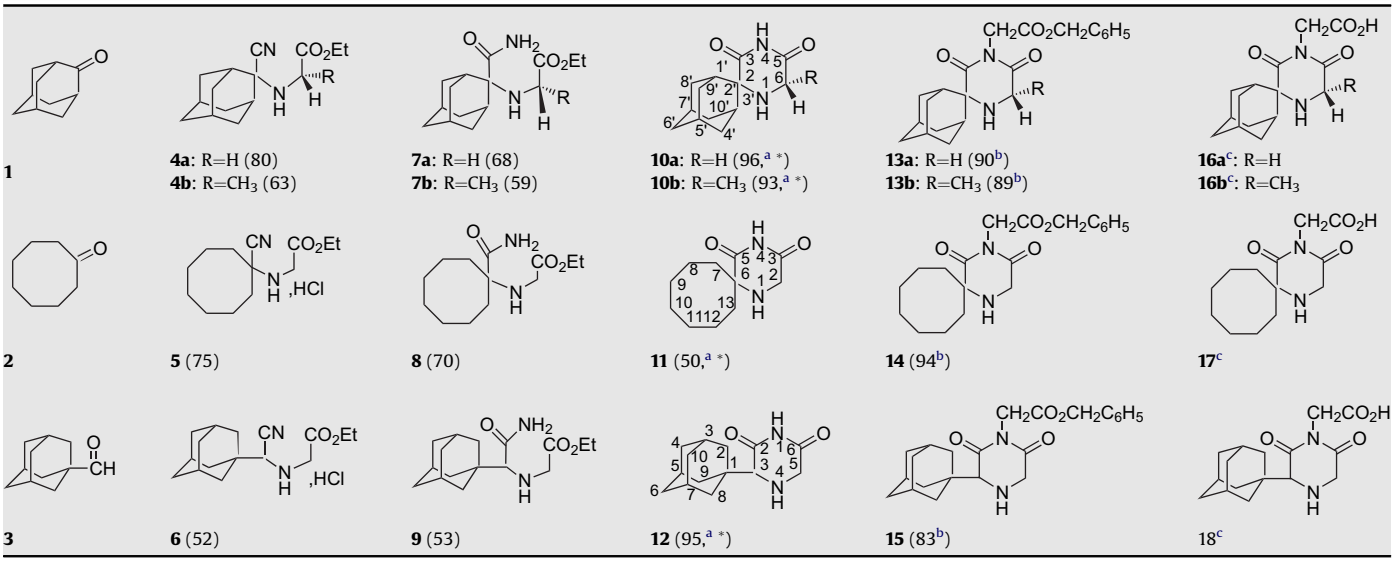
Table 1



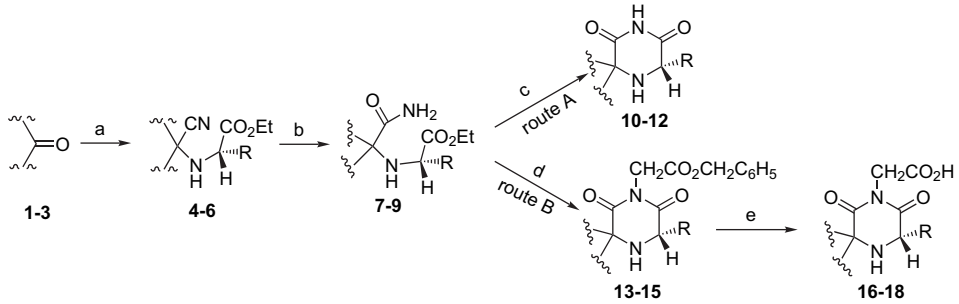
Yield in brackets.

The symbol asterisk (*) denotes the quantitative yield, obtained by following the procedure in Section 4.8.2.

[a] Yield obtained from the corresponding amido-ester compound using the procedure in Section 4.8.1.

[b] Yield based on the amido-ester compound used.

[c] Yield of debenzylation almost quantitative.



Scheme 1. Reagents and conditions: (a) NaCN, $H_2NCH_2CO_2Et\cdot HCl$ or $H_2NCH(CH_3)CO_2Et\cdot HCl$ (L-enantiomer), DMSO/H_2O (29:1), rt, 48 h and then $HCl_{(g)}/Et_2O$ only for the amino-nitriles **5** and **6** (Table 1); (b) (i) concd H_2SO_4, rt, 24 h; (ii) ice and then aq NH_3 26% to pH=8; (c) (i) $(Me_3Si)_2NK$, THF, 0–5 °C and then rt, 1 h, argon; (ii) HCl 5% to pH=4–5, 0–5 °C and then Na_2CO_3 to pH=7–8 or (ii) CF_3CO_2H (1 equiv); (d) (i) $(Me_3Si)_2NK$, THF, 0–5 °C and then rt, 1 h, argon; (ii) benzyl bromoacetate, DMF, rt, 48 h, argon; (e) H_2/Pd/C 10%, EtOH, 50 psi, rt, 3 h.

Herranz et al. have described a cyclization method involving the NaOH treatment, under phase transfer conditions, of one primary amido-ester precursor for 1 h, which led to the corresponding 1-unsubstituted 2,6-DKP in high yield.[7b] The 2,6-DKP cyclization precursor used was prepared via hydrolysis of the corresponding *N*-[(methoxycarbonyl)methyl]-α-amino nitrile, obtained by a modified Strecker synthesis. Although this synthetic pathway could be utilized as a general method to produce 1-unsubstituted 2,6-DKPs in good overall yields, to the best of our knowledge, it has not been reported whether it can be used to transform primary amide-ester 2,6-DKP precursors into 1-functionalized 2,6-DKPs directly. In a more recent paper, Herranz et al. described a NaH-mediated cyclization of a number of amido-ester precursors in THF to the corresponding 1-unsubstituted 2,6-DKPs in yields ranging from 20 to 95%.[7c] Surprisingly, in this paper the authors mentioned that the selective functionalization of the previous 2,6-DKPs at the imidic nitrogen in a separate reaction step, using alkyl halides and NaH as base in THF, gave the respective 1-substituted 2,6-DKPs in very poor yields and a complex mixture of side products. Another strategy was reported by Ugi et al.,[7d,e] according to which α-amino acids react with equimolar amount of an aldehyde or ketone and isocyanide in methanol to afford amido-ester derivatives in a reaction time of 3–14 days. These intermediates can be cyclized to 1-substituted 2,6-DKPs by refluxing them in THF for 3 days with potassium *tert*-butoxide in an approximate yield of 70%. When the Ugi coupling procedure was carried out using ketones under weak basic conditions (1 equiv of triethylamine), the formation of 2,6-DKPs was only observed in moderate to good yields, after a long reaction time. The Ugi multicomponent reaction is useful in producing 1-substituted 2,6-DKP derivatives; however, it is evident that this reaction cannot lead to the 1-unsubstituted 2,6-DKP compounds. Other syntheses of 1-substituted 2,6-DKPs including a base-promoted intramolecular cyclization (K_2CO_3, DMF, 70 °C) of amido-ester precursors (prepared in four steps from *N*-protected α-amino acids) both by solution-phase and by solid-phase methodologies have been reported.[7f] Apart from the problems associated with the configurational lability of the resulting 2,6-DKPs under cyclization reaction conditions, both methodologies suffer from low overall yields, while in some cases no 2,6-DKP was formed.

We herein wish to report an alternative synthetic approach to 2,6-DKP derivatives, which starts from ketones or aldehydes and proceeds smoothly in good overall yields, through a three step reaction sequence, as outlined in Scheme 1. In this approach, the key step of the imide formation was accomplished by employing a more efficient base-induced cyclization mode, involving the treatment of the amido-ester precursors **7**–**9** with an equivalent amount of

potassium bis(trimethysilyl)amide in THF at rt for a short reaction time. In comparison with the other bases, reported in the literature, the use of potassium bis(trimethylsilyl)amide allows synthesis of the 1-unsubstituted 2,6-DKPs **10**–**12** (route A) quantitatively as well as the functionalization at the imidic nitrogen of 2,6-DKPs **13**–**15** in one step and in excellent isolated yields (route B). It is noteworthy that the yields for compounds **10**–**12** dropped by 20–30% when sodium hydride was employed instead of potassium bis-(trimethylsilyl)amide under the same reaction conditions.

The synthetic pathway depicted in Scheme 1 could be generalized to obtain 2,6-DKP derivatives in high yields, by using cyclic or aliphatic aldehydes or ketones and a variety of α-amino acid esters as starting materials. The α-amino carboxamides **7**–**9** were the key intermediates in the synthesis of the 2,6-DKP derivatives **10**–**15** (Scheme 1). Given that α-amino carboxamides can be derived from their corresponding α-amino nitriles, we utilized the *N*-[(ethoxycarbonyl)methyl]-α-amino nitriles **4**–**6** in our synthetic strategy. The Strecker reaction is the most effective synthetic route leading to α-amino nitriles. Thus, the bulky carbonyl compounds **1**–**3** were reacted with the appropriate α-amino acid ethyl ester hydrochloride and NaCN in a DMSO/H_2O (29:1) mixture at rt to provide the corresponding α-amino nitriles **4**–**6** in moderate to high yields (Table 1). The α-amino nitriles **5** and **6**, in contrast with their counterparts **4a** and **4b**, were not stable enough to be purified by chromatography, and due to that, were precipitated as hydrochloride salts. It is also of note that the α-amino nitrile hydrochlorides **5** and **6** were unstable and decomposed on standing at rt. Subsequent acid-promoted hydrolysis of the α-amino nitriles **4**–**6** with concd H_2SO_4 at rt afforded the respective α-amino carboxamides **7**–**9** in 53–70% isolated yields. In the case of the α-amino nitrile **4a**, the corresponding hydrolysis product **7a** was formed along with its respective cyclization material **10a** in 5% yield. The small quantity of **10a** was easily separated by column chromatography.

Treatment of the precursor compounds **7**–**9** with potassium bis(trimethylsilyl)amide (1 equiv, THF, rt, 1 h) led to the corresponding 2,6-DKPs **10**–**12** in the form of potassium imidate salts. Eventually, the free 2,6-DKPs **10**–**12** were acquired by aq HCl (5%) treatment of their potassium salts followed by neutralization with Na_2CO_3 (route A). Using this procedure, the cyclooctane 2,6-DKP **11** was isolated in a significantly lower yield (50%) than those of the adamantane counterparts **10a**,**b** and **12**, which were obtained in very high yields (93–96%) (Table 1). Thus, we deduced that the lower yield of compound **11** was due to its higher instability (compared to **10a**,**b** and **12**) in the acidic aqueous medium. In fact, as shown in Table 1, all compounds **10**–**12** were obtained quantitatively (>99%) when their corresponding potassium salts were treated with equivalent amount of CF_3CO_2H in non-aqueous conditions (Section 4.8.2). Conversion of the amido-ester precursors **7**–**9** to the respective 1-functionalized 2,6-DKP analogues **13**–**15** was effected in excellent yields (83–94%) by treatment with potassium bis(trimethylsilyl)amide in THF and subsequent S_N2 reaction of the intermediate potassium imidate salts with benzyl bromoacetate in DMF within the same pot (route B). Finally, catalytic hydrogenolysis of the benzyl esters **13**–**15** yielded the corresponding carboxylic acids **16**–**18** quantitatively.

3. Conclusions

In this paper, we have developed mild and experimentally convenient protocols for construction of 2,6-DKP derivatives. In the critical step of our synthetic approach, amido-ester derivatives of the iminodiacetic acid can be readily transformed into 1-unsubstituted 2,6-DKPs quantitatively by a novel base-mediated cyclization methodology. The amido-ester 2,6-DKP precursors needed could be prepared either via Strecker synthesis followed by acid-promoted hydrolysis of the intermediate *N*-substituted α-amino nitriles, as described above, or by means of other syntheses mentioned elsewhere.[7a,b,8] Conversely to other base-mediated cyclization methodologies reported in the literature, ours offer the advantage that primary amido-ester 2,6-DKP precursors can be selectively converted to 1-functionalized 2,6-DKPs in one pot and in excellent yields. Particularly attractive is the facile synthesis of 1-carboxyalkylated 2,6-DKPs, which could be utilized as building blocks in the production of conformationally constrained peptidomimetics based on the 2,6-DKP scaffold. Applications in this direction have been achieved and will be published in due course.

4. Experimental section

4.1. General

Melting points were determined using a Büchi capillary apparatus and are uncorrected. FTIR spectra were recorded on a Perkin–Elmer RX 1 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker MSL 400 spectrometer, using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. Carbon multiplicities were established by DEPT experiments. The 2D NMR experiments (HMQC, COSY, and NOESY) were performed for the elucidation of the structures of the new compounds. Microanalyses were carried out by the Service Central de Microanalyse (CNRS), France, and the results obtained had a maximum deviation of ±0.4% from the theoretical value.

4.2. *N*-[2-Cyano(tricyclo[3.3.1.1^{3,7}]dec-2-yl)]glycine ethyl ester (4a): typical procedure

To a stirred suspension of NaCN (1.37 g, 27.9 mmol) and ethyl glycinate hydrochloride (3.9 g, 27.9 mmol) in 18 mL of DMSO/H_2O 9:1 (v/v), a solution of adamantanone (4 g, 26.6 mmol) in 36 mL DMSO was added in one portion. The reaction mixture was stirred at rt for 48 h in a stoppered flask and then poured into ice/water mixture (200 mL). The oily product formed was extracted with Et_2O (4×60 mL), and the combined extracts were washed with H_2O (4×50 mL) and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel (*n*-hexane/Et_2O 1:2) to afford pure amino nitrile **4a** (5.62 g, 80%) as white crystals; mp 73–75 °C (dec, Et_2O/*n*-pentane). IR (mull): ν 3314 (N–H), 2217 (C≡N), 1737 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=1.27 (t, 3H, J=7.0 Hz, OCH_2CH_3), 1.52 (d, 2H, J=11.8 Hz, H-4e, H-9e), 1.69 (s, 2H, H-6), 1.75 (s, 1H, H-5), 1.77–2.03 (complex m, 6H, H-1, H-3, H-7, H-8e, H-10e, N*H*), 2.13 (d, 2H, J=13.2 Hz, H-8a, H-10a), 2.21 (d, 2H, J=11.8 Hz, H-4a, H-9a), 3.49 (s, 2H, $HNCH_2CO_2C_2H_5$), 4.22 (q, 2H, J=7.0 Hz, CH_3CH_2O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.1 (*C*H_3), 26.5 (C-5), 26.7 (C-7), 30.3 (C-4, C-9), 34.5 (C-8, C-10), 34.6 (C-1, C-3), 37.3 (C-6), 45.1 ($HNCH_2CO_2C_2H_5$), 61.2 (CH_3CH_2O), 61.9 (C-2), 121.9 (*C*N), 171.4 (*C*$O_2C_2H_5$) ppm. Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.28; H, 8.37; N, 10.68.

4.3. (−)-*N*-[2-Cyano(tricyclo[3.3.1.1^{3,7}]dec-2-yl)]-L-alanine ethyl ester (4b)

From adamantanone (4 g, 26.6 mmol), ethyl L-alaninate hydrochloride (4.28 g, 27.9 mmol), and NaCN (1.37 g, 27.9 mmol). Purification of the crude product by column chromatography on silica gel (*n*-hexane/Et_2O 3:1, then 1:1) afforded pure amino nitrile **4b** (4.64 g, 63%) as white crystals; mp 43–45 °C (*n*-pentane). $[\alpha]_{589}^{28}$ −22.5 (*c* 0.4, $CHCl_3$). IR (mull): ν 3315 (N–H), 2218 (C≡N), 1728 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=1.27 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.34 (d, 3H, J=7.0 Hz, CH_3), 1.51 (d, 2H, J=11.3 Hz, H-4e,

H-9e), 1.70 (s, 2H, H-6), 1.76 (s, 1H, H-5), 1.79–2.05 (complex m, 6H, H-1, H-3, H-7, H-8e, H-10e, NH), 2.06–2.28 (complex m, 4H, H-4a, H-8a, H-9a, H-10a), 3.53 (q, 1H, J=7.0 Hz, HNC*H*$CO_2C_2H_5$), 4.20 (sym. m, 2H, CH_3CH_2O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.1 (CH_3CH_2O), 20.9 (CH_3), 26.5 (C-5), 26.6 (C-7), 30.3 (C-4), 30.5 (C-9), 34.0 (C-1), 34.2 (C-8), 34.7 (C-10), 36.0 (C-3), 37.4 (C-6), 51.6 (HNCHCO$_2$C$_2$H$_5$), 61.0 (CH_3CH_2O), 61.2 (C-2), 122.2 (CN), 175.4 ($CO_2C_2H_5$) ppm. Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.51; H, 8.62; N, 10.02.

4.4. *N*-[2-Aminocarbonyl(tricyclo[3.3.1.1^{3,7}]dec-2-yl)]glycine ethyl ester (7a): typical procedure

To the aminonitrile **4a** (2 g, 7.62 mmol), H_2SO_4 97% (3.6 mL) was added dropwise under ice cooling. After stirring at rt for 24 h, the mixture was poured into ice (30 g) and neutralized with aq NH_3 26%. The solid material formed was isolated by vacuum filtration, washed with H_2O (3×5 mL), dried, and finally purified by column chromatography on silica gel (Et_2O, then Et_2O/AcOEt 1:1) to afford the spirocyclic 2,6-DKP **10a** (90 mg, 5%) as a side product and then pure amino carboxamide **7a** (1.46 g, 68%) as a white crystalline solid; mp 115–117 °C (CH_2Cl_2/*n*-pentane). IR (mull): ν 3431, 3380, 3337, 3320, 3176, 1728, 1677, 1642 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.56 (d, 2H, J=12.3 Hz, H-4e, H-9e), 1.65 (s, 2H, H-6), 1.68–1.84 (m, 4H, H-5, H-7, H-8e, H-10e), 1.92–2.16 (m, 7H, H-1, H-3, H-4a, H-8a, H-9a, H-10a, N*H*CH_2), 3.30 (s, 2H, HNC*H*$_2$CO$_2$C$_2$H$_5$), 4.14 (q, 2H, J=7.1 Hz, CH_3CH_2O), 5.81 (br s, 1H, CONHH), 6.19 (br s, 1H, CONH*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.1 (CH_3), 26.6 (C-5), 27.0 (C-7), 32.1 (C-4, C-9), 32.5 (C-1, C-3), 34.5 (C-8, C-10), 37.6 (C-6), 43.7 (HNCH$_2$CO$_2$C$_2$H$_5$), 60.9 (CH_3CH_2O), 64.1 (C-2), 172.5 ($CO_2C_2H_5$), 176.9 ($CONH_2$) ppm. Anal. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.02; H, 8.60; N, 10.28.

4.5. (−)-*N*-[2-Aminocarbonyl(tricyclo[3.3.1.1^{3,7}]dec-2-yl)]-L-alanine ethyl ester (7b)

Amino nitrile **4b** (2.00 g, 7.24 mmol) was treated with H_2SO_4 97% (3.4 mL) according to the procedure described for the preparation of compound **7a**. After workup, the oily product formed was extracted with $CHCl_3$ (4×50 mL). The combined organic extracts were washed with H_2O (1×50 mL), dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The oily residue was chromatographed on a silica gel column (Et_2O, then Et_2O/AcOEt 1:1) to afford pure amino carboxamide **7b** (1.25 g, 59%) as white crystals; mp 111–113 °C (Et_2O). $[\alpha]_{589}^{29}$ −18.5 (*c* 0.2, $CHCl_3$). IR (mull): ν 3419, 3373, 3152, 1718, 1706, 1676 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.24 (d, 3H, J=7.0 Hz, C*H*$_3$), 1.46–1.60 (m, 2H, H-4e, H-9e), 1.64 (br s, 2H, H-6), 1.68–1.88 (m, 5H, H-5, H-7, H-8e, H-10e, N*H*CH), 1.90–2.06 (m, 3H, H-3, H-8a, H-10a), 2.08–2.17 (m, 2H, H-1, H-4a), 2.23 (dd, 1H, J=12.4, 2.8 Hz, H-9a), 3.46 (q, 1H, J=7.0 Hz, HNC*H*CO$_2$C$_2$H$_5$), 4.11 (q, 2H, J=7.1 Hz, CH_3CH_2O), 5.60 (br s, 1H, CONHH), 5.90 (br s, 1H, CONH*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.1 (CH_3CH_2O), 21.5 (CH_3), 26.8 (C-5), 26.9 (C-7), 32.1 (C-4), 32.2 (C-9), 32.6 (C-1), 33.8 (C-3), 34.4 (C-8), 34.7 (C-10), 37.6 (C-6), 49.9 (HNCHCO$_2$C$_2$H$_5$), 60.6 (CH_3CH_2O), 64.3 (C-2), 176.2 ($CO_2C_2H_5$), 177.4 ($CONH_2$) ppm. Anal. Calcd for $C_{16}H_{26}N_2O_3$: C, 65.28; H, 8.90; N, 9.52. Found: C, 65.34; H, 8.91; N, 9.71.

4.6. *N*-(1-Aminocarbonylcyclooctyl)glycine ethyl ester (8)

Cyclooctanone (3.36 g, 26.6 mmol), ethyl glycinate hydrochloride (3.90 g, 27.9 mmol), and NaCN (1.37 g, 27.9 mmol) were reacted according to the procedure described for the preparation of compound **4a**. After workup, the resulting dry Et_2O solution of the free amino nitrile **5** was treated with ethereal HCl under ice cooling. The precipitate was filtered off, washed with cold Et_2O (4×25 mL), and dried to afford amino nitrile hydrochloride **5** (5.50 g, 75%) as a white solid; mp 68–71 °C (dec). The IR and ^{1}H NMR spectrum of unpurified free amino nitrile **5** were measured. IR (film): ν 3329 (N–H), 2220 (C≡N), 1746 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.26 (t, 3H, J=7.0 Hz, OCH_2CH_3), 1.45–1.77 (m, 11H, H-3, H-4, H-5, H-6, H-7, N*H*), 1.80–1.97 (m, 4H, H-2, H-8), 3.49 (d, 2H, J=5.2 Hz, HNC*H*$_2$CO$_2$C$_2$H$_5$), 4.19 (q, 2H, J=7.0 Hz, CH_3CH_2O) ppm.

Title compound **8** was synthesized from the above amino nitrile hydrochloride **5** (2.90 g, 10.6 mmol) by treating with H_2SO_4 97% (5.5 mL) according to the procedure described for the preparation of compound **7a**. After workup, the white solid amino carboxamide **8** was collected by vacuum filtration, washed with H_2O (3×7 mL), and dried (1.90 g, 70%); mp 103–105 °C (CH_2Cl_2/*n*-pentane). IR (mull): ν 3421, 3341, 3308, 3195, 1731, 1658, 1606 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.25 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.34–1.69 (m, 12H, H-2, H-3, H-4, H-5, H-6, H-7, H-8), 1.82 (br s, 1H, N*H*CH_2), 2.02 (q, 2H, J=8.6, 9.8 Hz, H-2, H-8), 3.25 (s, 2H, HNC*H*$_2$CO$_2$C$_2$H$_5$), 4.16 (q, 2H, J=7.2 Hz, CH_3CH_2O), 5.36 (br s, 1H, CONHH), 7.15 (br s, 1H, CONH*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.1 (CH_3), 21.6 (C-4, C-6), 24.7 (C-5), 28.2 (C-3, C-7), 30.7 (C-2, C-8), 45.1 (HNCH$_2$CO$_2$C$_2$H$_5$), 61.1 (CH_3CH_2O), 64.3 (C-1), 172.3 ($CO_2C_2H_5$), 178.8 ($CONH_2$) ppm. Anal. Calcd for $C_{13}H_{24}N_2O_3$: C, 60.91; H, 9.44; N, 10.93. Found: C, 60.71; H, 9.36; N, 11.18.

4.7. *N*-[Aminocarbonyl(tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl] glycine ethyl ester (9)

1-Adamantanecarboxaldehyde **3** (2.00 g, 12.2 mmol) was reacted with ethyl glycinate hydrochloride (1.79 g, 12.8 mmol) and NaCN (627 mg, 12.8 mmol) according to the procedure described for the preparation of compound **4a**. After workup, the resulting dry Et_2O solution of free amino nitrile **6** was treated with ethereal HCl under ice cooling. The precipitated white hydrochloride **6**[9] was filtered off, washed with cold Et_2O (4×15 mL), and dried (1.98 g, 52%). Due to the instability of the amino nitrile hydrochloride **6** it was not possible to determine a clear mp.

Title compound **9** was synthesized from the above amino nitrile hydrochloride **6** (1.80 g, 5.75 mmol) by treating with H_2SO_4 97% (3.4 mL) according to the procedure described for the preparation of compound **7a**. After workup, the precipitate formed was filtered off, washed with cold H_2O (5×6 mL), dried, and then chromatographed on a silica gel column (AcOEt) to afford pure amino carboxamide **9** (900 mg, 53%) as a white crystalline solid; mp 119–121 °C (AcOEt/*n*-pentane). IR (mull): ν 3426, 3339, 3313, 3185, 1731, 1668, 1624 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.23 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.52–1.75 (m, 12H, H-2, H-4, H-6, H-8, H-9, H-10), 1.97 (s, 3H, H-3, H-5, H-7), 2.14 (br s, 1H, N*H*CH_2), 2.62 (s, 1H, HNC*H*CONH$_2$), 3.18 (d, 1H, J_{AB}=17.6 Hz, HNC*H*$_{2A}$CO$_2$C$_2$H$_5$), 3.41 (d, 1H, J_{AB}=17.6 Hz, HNC*H*$_{2B}$CO$_2$C$_2$H$_5$), 4.14 (q, 2H, J=7.2 Hz, CH_3CH_2O), 5.86 (br s, 1H, CONHH), 6.71 (br s, 1H, CONH*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.1 (CH_3), 28.4 (C-3, C-5, C-7), 35.2 (C-1), 36.8 (C-4, C-6, C-10), 39.2 (C-2, C-8, C-9), 49.7 (HNCH$_2$CO$_2$C$_2$H$_5$), 61.0 (CH_3CH_2O), 73.2 (NHCHCONH$_2$), 172.2 ($CO_2C_2H_5$), 174.8 ($CONH_2$) ppm. Anal. Calcd for $C_{16}H_{26}N_2O_3$: C, 65.28; H, 8.90; N, 9.52. Found: C, 65.40; H, 8.98; N, 9.28.

4.8. General procedures for the synthesis of compounds 10–12

4.8.1. General procedure I

Potassium bis(trimethylsilyl)amide (2 mmol) was added portionwise to a stirred solution of the appropriate amide-esters **7–9** (2 mmol) in dry THF (20 mL) under ice cooling. After stirring at rt for 1 h, under argon, the reaction mixture was evaporated to dryness under reduced pressure. To the remaining white solid

(potassium imidate salt), H_2O (5 mL) was added and the mixture was slowly quenched with HCl 5% to pH=4–5 under cooling and then adjusted to pH=7–8 with solid Na_2CO_3. The white precipitate formed was isolated by vacuum filtration, washed with H_2O (5 mL), and dried. TLC showed one spot only corresponding to the desired 2,6-diketopiperazines **10–12** (Table 1).

4.8.2. General procedure II

Potassium bis(trimethylsilyl)amide (2 mmol) was added portionwise to the appropriate amide-esters **7–9** (2 mmol), dissolved in dry THF (20 mL) under ice cooling. After stirring at rt for 1 h under argon, trifluoroacetic acid (1 equiv) was added to the reaction mixture. The solvent was then evaporated under reduced pressure, and the white solid residue was filtered through a short column of silica gel, using a mixture of AcOEt/Et_2O 1:1 as eluent, to afford the corresponding 1-unsubstituted 2,6-diketopiperazines **10–12** in quantitative yield (Table 1).

*4.8.2.1. Spiro[piperazine-2,2′-tricyclo[3.3.1.1^{3,7}]decane]-3,5-dione (**10a**).* White crystals; yield >99%; mp 196–198 °C ($CHCl_3$/*n*-pentane). IR (mull): ν 3328, 3194, 3098, 1721, 1682 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.52 (d, 2H, *J*=12.4 Hz, H-4′e, H-9′e), 1.65 (s, 1H, H-1), 1.70–2.02 (complex m, 8H, H-1′, H-3′, H-5′, H-6′, H-7′, H-8′e, H-10′e), 2.25 (d, 2H, *J*=12.4 Hz, H-4′a, H-9′a), 2.32 (d, 2H, *J*=12.8 Hz, H-8′a, H-10′a), 3.62 (s, 2H, H-6), 7.83 (br s, 1H, H-4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=27.0 (C-5′), 27.2 (C-7′), 32.3 (C-4′, C-9′), 32.4 (C-1′, C-3′), 33.1 (C-8′, C-10′), 38.0 (C-6′), 44.1 (C-6), 60.5 (C-2,2′), 173.1, 174.8 (C-3, C-5) ppm. Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.59; H, 7.51; N, 12.07.

*4.8.2.2. (−)-S-6-Methylspiro[piperazine-2,2′-tricyclo[3.3.1.1^{3,7}]decane]-3,5-dione (**10b**).* White crystals; yield >99%; mp 190–192 °C (CH_2Cl_2/*n*-pentane). $[\alpha]_{589}^{29}$ −14 (*c* 0.2, $CHCl_3$). IR (mull): ν 3298, 3186, 3088, 1719, 1677 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.28 (br s, 1H, H-1), 1.42 (d, 3H, *J*=7.0 Hz, C*H*$_3$), 1.47–1.58 (sym m, 2H, H-4′e, H-9′e), 1.62–1.94 (complex m, 8H, H-3′, H-5′, H-6′, H-7′, H-8′, H-10′e), 2.08 (s, 1H, H-1′), 2.16 (d, 1H, *J*=11.2 Hz, H-4′a), 2.35 (d, 1H, *J*=12.6 Hz, H-9′a), 2.93 (d, 1H, *J*=12.9 Hz, H-10′a), 3.61 (br d, 1H, *J*=5.4 Hz, H-6), 7.69 (br s, 1H, H-4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.4 (*C*H$_3$), 27.0 (C-5′), 27.2 (C-7′), 30.8 (C-1′), 31.5 (C-4′), 32.6 (C-8′), 33.2 (C-9′), 33.8 (C-10′), 34.7 (C-3′), 38.0 (C-6′), 48.7 (C-6), 61.4 (C-2,2′), 175.2, 175.5 (C-3, C-5) ppm. Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.67; H, 8.17; N, 11.22.

*4.8.2.3. 1,4-Diazaspiro[5,7]tridecane-3,5-dione (**11**).* White crystals; yield >99%; mp 213–215 °C ($CHCl_3$/Et_2O). IR (mull): ν 3326, 3176, 3063, 1734, 1671 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.42–1.80 (complex m, 13H, H-1, H-7, H-8, H-9, H-10, H-11, H-12, H-13), 2.02–2.19 (m, 2H, H-7, H-13), 3.64 (s, 2H, H-2), 7.77 (br s, 1H, H-4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.3 (C-9, C-11), 24.7 (C-10), 28.0 (C-8, C-12), 30.6 (C-7, C-13), 45.0 (C-2), 59.8 (C-6), 172.0, 176.7 (C-3, C-5) ppm. Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.96; H, 8.59; N, 13.19.

*4.8.2.4. 3-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)-2,6-piperazinedione (**12**).* White crystals; yield >99%; mp 207–209 °C (dec, AcOEt). IR (mull): ν 3314, 3195, 3082, 1725, 1687 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.61–1.76 (m, 10H, H-2, H-4, H-6, H-8, H-9, H-10 adamantane, H-4 piperazine), 1.85 (d, 3H, *J*=10.8 Hz, part of quartet, H-2, H-8, H-9 adamantane), 2.00 (s, 3H, H-3, H-5, H-7 adamantane), 2.98 (s, 1H, H-3 piperazine), 3.53 (d, 1H, J_{AB}=18.3 Hz, H_A-5 piperazine), 3.77 (d, 1H, J_{AB}=18.3 Hz, H_B-5 piperazine), 8.00 (br s, 1H, H-1 piperazine) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.4 (C-3, C-5, C-7 adamantane), 36.7 (C-4, C-6, C-10 adamantane), 37.2 (C-1 adamantane), 39.4 (C-2, C-8, C-9 adamantane), 48.4 (C-5 piperazine), 66.0 (C-3 piperazine), 172.0 (C-2, C-6 piperazine) ppm. Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.68; H, 8.15; N, 11.34.

4.9. General procedure for the synthesis of compounds 13a–15

The appropriate amido-ester precursors **7a–9** (2 mmol) were treated with potassium bis(trimethylsilyl)amide (2 mmol) in dry THF (20 mL) at rt for 1 h under argon, as described above. The solvent was then evaporated under reduced pressure and the remaining white solid (potassium imidate salt) was dissolved in dry DMF (10 mL). To this solution, benzyl bromoacetate (2.1 mmol) dissolved in dry DMF (5 mL) was added dropwise. After being stirred at rt for 48 h under argon, the reaction mixture was poured into an ice/water mixture (40 mL) and extracted with Et_2O (4×35 mL). The organic phase was washed with brine (35 mL), dried (Na_2SO_4), and evaporated under reduced pressure affording crude compounds **13a–15**, which were purified by column chromatography on silica gel, using EtOAc/*n*-hexane mixtures as eluents (1:2, 1:6, 1:1, and 2:1).

*4.9.1. 3,5-Dioxospiro[piperazine-2,2′-tricyclo[3.3.1.1^{3,7}]decane]-4-acetic acid benzyl ester (**13a**)*

White crystals; yield 90% (0.69 g); mp 111–112 °C (Et_2O/*n*-pentane). IR (mull): ν 3310, 1740, 1722, 1690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.52 (d, 2H, *J*=12.9 Hz, H-4′e, H-9′e), 1.69 (br s, 5H, H-1, H-6′, H-8′e, H-10′e), 1.83 (s, 1H, H-5′), 1.87 (s, 1H, H-7′), 1.98 (s, 2H, H-1′, H-3′), 2.27 (d, 4H, *J*=12.7 Hz, H-4′a, H-8′a, H-9′a, H-10′a), 3.72 (s, 2H, H-6), 4.51 (s, 2H, C*H*$_2$CO$_2$CH$_2$Ph), 5.13 (s, 2H, CH$_2$CO$_2$C*H*$_2$Ph), 7.26–7.37 (m, 5H, H-aromatic) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=27.0 (C-5′), 27.2 (C-7′), 32.3 (C-4′, C-9′), 32.6 (C-1′, C-3′), 33.1 (C-8′, C-10′), 38.0 (C-6′), 40.6 (*C*H$_2$CO$_2$CH$_2$Ph), 44.4 (C-6), 60.5 (C-2,2′), 67.2 (CH$_2$CO$_2$CH$_2$Ph), 128.2 (C-4 aromatic), 128.4 (C-3, C-5 aromatic), 128.6 (C-2, C-6 aromatic), 135.1 (C-1 aromatic), 168.0 (*C*O$_2$CH$_2$Ph), 172.1, 174.3 (C-3, C-5) ppm. Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.84; H, 7.02; N, 7.06.

*4.9.2. (−)-(S)-6-Methyl-3,5-dioxospiro[piperazine-2,2′-tricyclo[3.3.1.1^{3,7}]decane]-4-acetic acid benzyl ester (**13b**)*

Colorless viscous oil; yield 89% (0.71 g); $[\alpha]_{589}^{29}$ −10.5 (*c* 0.2, $CHCl_3$). IR (film): ν 3305, 1754, 1725, 1681 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.25 (br s, 1H, H-1), 1.42 (d, 3H, *J*=7.0 Hz, C*H*$_3$), 1.51 (t, 2H, *J*=10.8 Hz, H-4′e, H-9′e), 1.60–1.73 (m, 5H, H-6′, H-8′, H-10′e), 1.82 (s, 1H, 5′-H), 1.86 (s, 2H, H-3′, H-7′), 2.07 (s, 1H, H-1′), 2.14 (d, 1H, *J*=12.4 Hz, H-4′a), 2.39 (d, 1H, *J*=12.6 Hz, H-9′a), 2.88 (d, 1H, *J*=12.9 Hz, H-10′a), 3.71 (q, 1H, *J*=6.9 Hz, H-6), 4.39 (d, 1H, J_{AB}=16.7 Hz, CH_{2A}CO$_2$CH$_2$Ph), 4.60 (d, 1H, J_{AB}=16.7 Hz, CH_{2B}CO$_2$CH$_2$Ph), 5.12 (s, 2H, CH$_2$CO$_2$C*H*$_2$Ph), 7.26–7.42 (m, 5H, H-aromatic) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.5 (*C*H$_3$), 27.0 (C-5′), 27.2 (C-7′), 30.9 (C-1′), 31.5 (C-4′), 32.5 (C-8′), 33.1 (C-9′), 33.9 (C-10′), 34.9 (C-3′), 38.0 (C-6′), 41.0 (*C*H$_2$CO$_2$CH$_2$Ph), 49.2 (C-6), 60.9 (C-2,2′), 67.2 (CH$_2$CO$_2$CH$_2$Ph), 128.3 (C-4 aromatic), 128.4 (C-3, C-5 aromatic), 128.5 (C-2, C-6 aromatic), 135.1 (C-1 aromatic), 168.1 (*C*O$_2$CH$_2$Ph), 174.6, 175.1 (C-3, C-5) ppm. EM-ES, *m*/*z* 397.3 (30) $[M+1]^+$. Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12; N, 7.07. Found: C, 69.37; H, 7.22; N, 7.35.

*4.9.3. 3,5-Dioxo-1,4-diazaspiro[5.7]tridecane-4-acetic acid benzyl ester (**14**)*

White crystals; yield 94% (0.67 g); mp 80–82 °C (Et_2O/*n*-pentane). IR (mull): ν 3308, 1747, 1719, 1673 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.44–1.78 (m, 13H, H-1, H-7, H-8, H-9, H-10, H-11, H-12, H-13), 2.11 (q, 2H, *J*=8.8 Hz, H-7, H-13), 3.75 (s, 2H, H-2), 4.53 (s, 2H, C*H*$_2$CO$_2$CH$_2$Ph), 5.14 (s, 2H, CH$_2$CO$_2$C*H*$_2$Ph), 7.30–7.46 (m, 5H, H-aromatic) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.2 (C-9, C-11), 24.7 (C-10), 27.9 (C-8, C-12), 30.9 (C-7, C-13), 40.0 (*C*H$_2$CO$_2$CH$_2$Ph), 45.1

(C-2), 59.9 (C-6), 67.3 ($CH_2CO_2CH_2Ph$), 128.3 (C-4 aromatic), 128.4 (C-3, C-5 aromatic), 128.6 (C-2, C-6 aromatic), 135.1 (C-1 aromatic), 167.8 (CO_2CH_2Ph), 171.2, 176.1 (C-3, C-5) ppm. Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.14; H, 7.39; N, 7.56.

4.9.4. 3-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)-2,6-dioxopiperazine-1-acetic acid benzyl ester (**15**)

White crystals; yield 83% (0.66 g); mp 106–108 °C (Et_2O/*n*-pentane). IR (mull): ν 3339, 1745, 1727, 1669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.62–1.78 (m, 9H, H-2, H-4, H-6, H-8, H-9, H-10 adamantane), 1.80 (br s, 1H, H-4 piperazine), 1.86 (d, 3H, J=12.4 Hz, part of quartet, H-2, H-8, H-9 adamantane), 2.00 (br s, 3H, H-3, H-5, H-7 adamantane), 3.09 (s, 1H, H-3 piperazine), 3.64 (d, 1H, J_{AB}=18 Hz, H_A-5 piperazine), 3.91 (d, 1H, J_{AB}=18 Hz, H_B-5 piperazine), 4.52 (d, 1H, J_{AB}=16.8 Hz, $CH_{2A}CO_2CH_2Ph$), 4.59 (d, 1H, J_{AB}=16.8 Hz, $CH_{2B}CO_2CH_2Ph$), 5.17 (s, 2H, $CH_2CO_2CH_2Ph$), 7.30–7.41 (m, 5H, H-aromatic) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=27.6 (C-3, C-5, C-7 adamantane), 35.9 (C-4, C-6, C-10 adamantane), 36.7 (C-1 adamantane), 38.5 (C-2, C-8, C-9 adamantane), 39.2 ($CH_2CO_2CH_2Ph$), 48.0 (C-5 piperazine), 65.5 (C-3 piperazine), 66.4 ($CH_2CO_2CH_2Ph$), 127.3 (C-4 aromatic), 127.5 (C-3, C-5 aromatic), 127.7 (C-2, C-6 aromatic), 134.2 (C-1 aromatic), 166.8 (CO_2CH_2Ph), 170.3, 170.4 (C-2, C-6 piperazine) ppm. Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12; N, 7.07. Found: C, 69.50; H, 7.27; N, 6.90.

4.10. General procedure for the hydrogenolysis of the benzyl esters 13a–15 to the corresponding carboxylic acids 16a–18

A solution of the appropriate benzyl esters **13a**–**15** (2 mmol) in abs EtOH was hydrogenated for 3 h at rt and 50 psi pressure in the presence of 10% Pd/C. The catalyst was filtered off, washed with portions of hot MeOH (3×15 mL), and the combined filtrates were evaporated under reduced pressure to yield the corresponding carboxylic acids **16a**–**18**.

4.10.1. 3,5-Dioxospiro[piperazine-2,2′-tricyclo[3.3.1.1^{3,7}]decane]-4-acetic acid (**16a**)

White solid; yield >99%; mp 206–208 °C (dec, EtOH/Et_2O). IR (mull): ν 3334, 1749, 1729, 1630 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ=1.44 (d, 2H, J=12.1 Hz, H-4′e, H-9′e), 1.63 (d, 2H, J=11.5 Hz, H-8′e, H-10′e), 1.65 (s, 2H, H-6′), 1.76 (s, 1H, H-5′), 1.80 (s, 1H, H-7′), 1.94 (s, 2H, H-1′, H-3′), 2.25 (td, 4H, J=13.3, 14.5 Hz, H-4′a, H-8′a, H-9′a, H-10′a), 2.80–3.91 (v br s, 2H, CO_2H, N*H*, under DMSO water peak), 3.59 (s, 2H, H-6), 4.27 (s, 2H, CH_2CO_2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=26.6 (C-5′), 26.9 (C-7′), 31.8 (C-1′, C-3′), 32.0 (C-4′, C-9′), 32.7 (C-8′, C-10′), 37.8 (C-6′), 40.3 (CH_2CO_2H), 43.9 (C-6), 59.4 (C-2, 2′), 169.3 (CO_2H), 172.2, 174.4 (C-3, C-5) ppm. Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.85; H, 6.98; N, 9.39.

4.10.2. (−)-(S)-6-Methyl-3,5-dioxospiro[piperazine-2,2′-tricyclo[3.3.1.1^{3,7}]decane]-4-acetic acid (**16b**)

White solid; yield >99%; mp 132–134 °C (Et_2O/*n*-pentane). $[\alpha]_{589}^{28}$ −17.5 (*c* 0.2, $CHCl_3$). IR (mull): ν 3306, 1726, 1686 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.43 (d, 3H, J=6.9 Hz, CH_3), 1.47–1.59 (sym. m, 2H, H-4′e, H-9′e), 1.61–1.77 (m, 5H, H-6′, H-8′, H-10′e), 1.83 (s, 1H, H-5′), 1.87 (s, 2H, H-3′, H-7′), 2.09 (s, 1H, H-1′), 2.13 (d, 1H, J=15.2 Hz, H-4′a), 2.36 (d, 1H, J=12.4 Hz, H-9′a), 2.88 (d, 1H, J=12.7 Hz, H-10′a), 3.73 (q, 1H, J=6.9 Hz, H-6), 4.38 (d, 1H, J_{AB}=17.1 Hz, $CH_{2A}CO_2H$), 4.53 (d, 1H, J_{AB}=17.1 Hz, $CH_{2B}CO_2H$), 5.76 (br s, 2H, CO_2H, N*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.4 (CH_3), 27.0 (C-5′), 27.2 (C-7′), 30.9 (C-1′), 31.5 (C-4′), 32.5 (C-8′), 33.0 (C-9′), 33.9 (C-10′), 34.8 (C-3′), 38.0 (C-6′), 40.7 (CH_2CO_2H), 49.1 (C-6), 61.0 (C-2,2′), 173.6 (CO_2H), 174.4, 175.0 (C-3, C-5) ppm. Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.15. Found: C, 62.69; H, 7.34; N, 9.27.

4.10.3. 3,5-Dioxo-1,4-diazaspiro[5.7]tridecane-4-acetic acid (**17**)

White solid; yield >99%; mp 201–203 °C (dec, MeOH/Et_2O). IR (mull): ν 2472–2008, 1749, 1693, 1569 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ=1.47 (br s, 8H, H-8, H-9, H-10, H-11, H-12), 1.55–1.70 (m, 4H, H-7, H-9, H-11, H-13), 1.96 (q, 2H, J=9.0 Hz, H-7, H-13), 3.58 (s, 2H, H-2), 3.85 (br s, 2H, CO_2H, N*H*), 4.24 (s, 2H, CH_2CO_2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=21.3 (C-9, C-11), 24.7 (C-10), 28.0 (C-8, C-12), 30.5 (C-7, C-13), 40.0 (CH_2CO_2H), 44.9 (C-2), 59.4 (C-6), 169.6 (CO_2H), 171.9, 176.5 (C-3, C-5) ppm. Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 57.98; H, 7.47; N, 10.21.

4.10.4. 3-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)-2,6-dioxopiperazine-1-acetic acid (**18**)

White solid; yield >99%; mp 206–208 °C (dec, EtOH/Et_2O). IR (mull): ν 3348, 1752, 1731, 1637 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ=1.56–1.74 (m, 9H, H-2, H-4, H-6, H-8, H-9, H-10 adamantane), 1.81 (d, 3H, J=12.0 Hz, part of quartet, H-2, H-8, H-9 adamantane), 1.93 (s, 3H, H-3, H-5, H-7 adamantane), 3.04 (s, 1H, H-3 piperazine), 3.15–3.48 (v br s, 2H, CO_2H, N*H*, under DMSO water peak), 3.55 (d, 1H, J_{AB}=18.3 Hz, H_A-5 piperazine), 3.67 (d, 1H, J_{AB}=18.3 Hz, H_B-5 piperazine), 4.27 (s, 2H, CH_2CO_2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=27.9 (C-3, C-5, C-7 adamantane), 36.4 (C-4, C-6, C-10 adamantane), 36.9 (C-1 adamantane), 38.8 (C-2, C-8, C-9 adamantane), 39.6 (CH_2CO_2H), 48.3 (C-5 piperazine), 65.2 (C-3 piperazine), 169.0 (CO_2H), 171.7, 171.8 (C-2, C-6 piperazine) ppm. Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.15. Found: C, 62.85; H, 7.32; N, 8.88.

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