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Synthesis of new molecular scaffolds: 3-aza-7,9-dioxa-bicyclo[4.2.1]nonane (8-*exo* BTKa) and 3-aza-8,10-dioxa-bicyclo[5.2.1]decane (9-*exo* BTKa) carboxylic acids

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Abstract—Two classes of enantiopure molecular scaffolds were prepared, whose lactam structure formally derives from the coupling between tartaric acid and β- or γ-ketoamines. We labelled these compounds as 8-*exo* and 9-*exo* BTKa, indicating the lactam size (8- and 9-membered ring, respectively). Starting from β- and γ-nitroketones, the synthesis involves the ketal formation by (*R*,*R*)-dimethyl tartrate. The subsequent amide bond formation occurs during the hydrogenation of the nitro group over Raney-Ni and no expected open chain amine was observed.

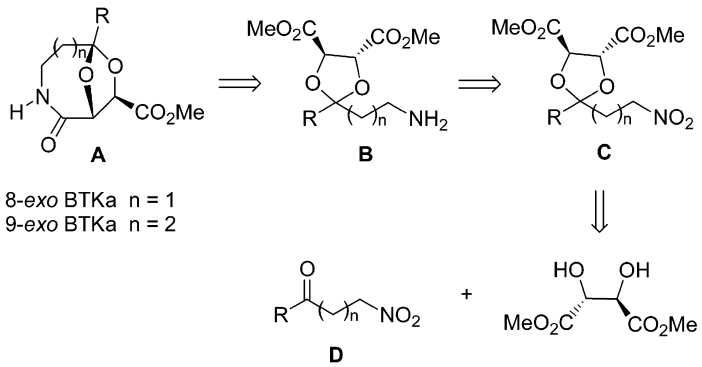
1. Introduction

We recently reported on the synthesis of two new classes of conformationally restricted dipeptide isosteres, whose synthesis is based on the combination of a tartaric acid derivative and either α-amino aldehydes[1] or α-amino-ketones.[1b,2] For the sake of simplicity, we named these compounds BTAa[3] (**1a**–**b**) and BTKa[4] (**2a**–**b**), respectively. Their general structure is reported in Figure 1.

$R_1 = H$	7-exo BTAa, **1a**	7-endo BTAa, **1b**
$R_1 \neq H$	7-exo BTKa, **2a**	7-endo BTKa, **2b**

Figure 1. General structure of peptide isosteres BTAa and BTKa.

Both classes of compounds have some interesting features, commonly required in designing new peptide isosteres: the synthesis starts from commercially available enantiopure precursors; the stereochemistry can be controlled by choosing the suitable α-amino acid or tartaric acid derivative; they are compatible with solid phase synthesis techniques.[5] The 7-*endo* BTAa isosteres (**1b**) proved to be efficient reverse turn inducers in a peptide chain.[1b,5,6] Furthermore, these compounds found an application as monomers for the generation of oligomers[7] and as chiral auxiliares.[8]



Scheme 1. Retrosynthetic analysis of 8-*exo* and 9-*exo* BTKa.

Keywords: Ketal; Nitroketone; Peptidomimetic; Tartaric acid.
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With the aim to extend the methodology to new structures of the BTKa family by ring enlargement from 7-membered one (**2a**–**b**) up to the size of 8 and 9, we envisaged a retrosynthetic approach (Scheme 1), where the formation of the ketal (**B**) between the tartaric moiety and an amino-ketone precedes the ring closure through the amide bond (**A**).

To avoid the formation of Schiff bases and facilitate the ketalisation process, the amino group needs to be protected. Therefore, β- and γ-nitroketones (**D**) were used as starting materials, where the nitro group masks the amine function needed for the amide bond formation.

Furthermore, we were encouraged on the possible success of the envisaged strategy by an analogue example reported by Levine et al.[9] In their paper, the authors used *o*-nitro-benzaldehyde as starting material to be coupled with (*R*,*R*)-diethyl tartrate to obtain the cyclic compound **3** (Fig. 2).

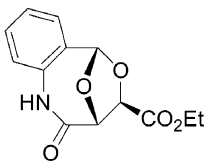

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Figure 2. Structure of the compound synthesised by Levine and co-workers.[9]

However, there is an important difference with our case: we used ketones instead of aldehydes and the nitro group was bound to an aliphatic chain. Probably due to these differences in substrates, during the synthesis we encountered a few problems that did not occur to Levine et al. These will be reported in details in the next section.

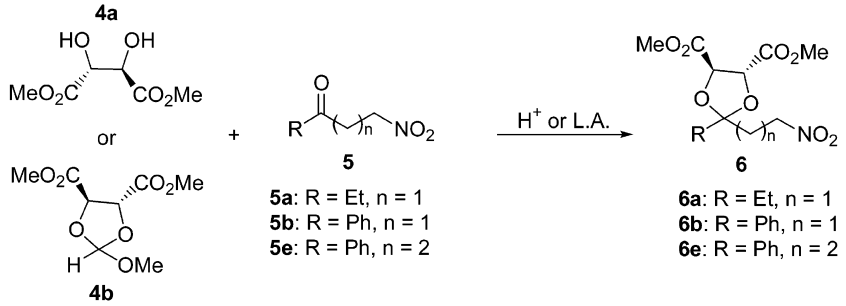
2. Results and discussion

With respect to the previously published methodology,[1a,2] we inverted the order of the two key steps of the synthesis, i.e. the formation first of the ketal with the tartaric moiety and then of the amide bond to close the ring.

Although the preparation of ketals with tartaric acid is extensively reported, the ketalisation of β- or γ-nitroketones is not as straightforward as one would expect it to be.

The reaction, reported in Scheme 2, has been performed under many conditions, summarised in Table 1.

The classical ketalisation reaction, employing **4a** as a diol and **5b** as a substrate,[9] was performed under acidic catalysis and Dean–Stark azeotropic distillation, affording the unreacted starting material (entry 1). Because of this unexpected result, we experimented alternative methods, employing trimethyl orthoformate as dehydrating agent (entry 2).[10] Starting from **4a** and **5b** in a 2:1 ratio, in the presence of 2 equiv. of $HC(OMe)_3$ under MsOH catalysis at 100 °C for 3 h, unreacted **5b** was recovered, whereas the dimethyl tartrate **4a** was transformed into **4b**. This activated form of tartaric acid has been used in *trans*-ketalisation reactions, as exemplified by the synthesis reported by Giordano et al.,[11] where, in order to obtain a cyclic ketals with dimethyl tartrate, **4a** was first converted into **4b** and then added to the substrate. Performing the reaction under



Scheme 2. Ketalisation with (*R*,*R*)-dimethyl tartrate or its derivative. The reaction conditions are reported in Table 1.

Table 1. Ketal formation with (*R*,*R*)-dimethyl tartrate or its derivative under acidic catalysis

Entry	Substrate	(*R*,*R*)-**4** (eq)	Eq $HC(OMe)_3$	Solvent	Temp. (°C)	Time (h)	H^+ or L.A. (%)	Products (%)
1	**5b**	**4a** (1)	None	Benzene	Reflux	30	*p*-TsOH (5)	nr[a]
2		**4a** (2)	2	None	100	3	MsOH (7)	**4b**
3		**4b** (1)	None	DCM	25	48	H_2SO_4 (30)	**6b** (35)
4		**4b** (1.2)	2	DCM	25	88	H_2SO_4 (23)	**6b** (25)
5		**4b** (1.3)	4	DCM	25	136	H_2SO_4 (23)	**6b** (35)
6		**4b** (1)	2	DCM	25	60	MsOH (10)	**4a**
7		**4b** (1)	None	DCM	25	60	Amberlyst15 (25 w/w)	nr[a]
8	**5a**	**4b** (1.3)	None	DM	25	36	H_2SO_4 (23)	**6a** (36)
9	**5e**	**4b** (1.5)	None	DCM	25	24	H_2SO_4 (23)	**6e** (44)
10		**4b** (1.3)	None	DCM	25	48	H_2SO_4 (23)	**6e** (74)
11	**5a**	**4a** (1.2)	1.2	ACN	25	19	$Sc(OTf)_3$ (10)	**6a** (60)
12	**5b**	**4a** (1.2)	1.2	ACN	25	48	$Sc(OTf)_3$ (10)	**6b** (22)
13		**4a** (1.1)	None	DCM	25	48	$In(Otf)_3$ (10)	nr[a]

[a] No reaction.

the reported conditions[11] on **5b** in DCM at room temperature and under H_2SO_4 catalysis, **6b** was eventually obtained in 35% yield after 48 h, together with unreacted **5b** (entry 3). Based on this result, we tried to increase the reaction conversion by increasing the **4b**:**5b** ratio, the reaction time and the amount of $HC(OMe)_3$ in the reaction mixture (entries 4 and 5). In both cases the conversion never exceeded 35%.

The change of acid catalyst from H_2SO_4 to MsOH (entry 6) or to the sulphonic resin Amberlyst15 (entry 7) proved to be inefficient towards the *trans*-ketalisation and resulted in the hydrolysis of **4b** or no reaction at all, respectively.

The reaction performed under the best conditions found so far (entry 3) on the aliphatic substrate **5a**, afforded **6a** in 36% yield (entry 8). This unreactivity cannot be attributed only to the reluctance of the substrate **5b** to break the conjugation of its enone moiety, since the same behaviour was found in the case of the aliphatic nitroketone **5a**. Furthermore, the reaction proved much more efficient on the aromatic substrate **5e**, affording **6e** in 44% yield (entry 9). Conversion increased up to 74% (entry 10), simply by extending the reaction time from 24 to 48 h.

Since the use of protic acids as catalysts afforded unsatisfying results, at least in the case of β-nitroketones **5a** and **5b**, we decided to explore the use of Lewis acids instead.

Scandium triflate and scandium triflimide promote ketalisation and *trans*-ketalisation reactions, under very mild conditions and in very good yields.[12]

In their paper, Ishihara et al.[12] report that $Sc(OTf)_3$ gives better results in the reaction of ketones with diethyl tartrate. In our case, we had to increase the amount of catalyst up to 10% (using the advised 1% quantity gave no result; data not shown) and the conversion, if fairly good in the case of aliphatic ketone **5a** (60%, Entry 11), was disappointing in the case of aromatic **5b** (22%, entry 12). The last attempt using $In(OTf)_3$ as catalyst resulted in the recovery of the starting material **5b** (entry 13), as actually expected since this method has in fact been reported for thio- and *trans*-thioketalisations.[13]

Unfortunately, when we repeated the reaction under the best conditions found for each substrate, we always got different results. Since the reaction represented in Scheme 1 is an equilibrium and we did not find a way to shift it towards the products, we must, therefore, assume that minimal variations of the reaction conditions, normally unperceptable by the operator, have great influence on the outcome of the reaction.

Thus, the real obstacle to the formation of the ketal could be the proximity of the nitro group to the carbonyl. This is probably due to the keto–enol and nitro–isonitro tautomerisms contemporarily present in the substrates (i.e., β-nitroketones) that form an extended conjugate species that does not easily undergo the ketalisation. The effect is increased in aromatic substrates. This hypothesis seems to be confirmed when α-nitroacetophenone is used as substrate (this would afford 7-*exo* BTKa, **2a**), since in all cases the unreacted starting material is recovered (data not shown). Furthermore, in the case of γ-nitroketones, the presence of an additional methylene unity between the carbonyl and the nitro group (from **5b** to **5e**) breaks the extended conjugation of the substrate, resulting in much higher conversion (from 35 to 74%).

Therefore, considering that in all cases the carbonyl group must be activated in some way towards the attack by the hydroxyls belonging to the tartaric acid derivative, we decided to synthesise and isolate first the dimethyl ketal of each substrate on which to perform a *trans*-ketalisation reaction.

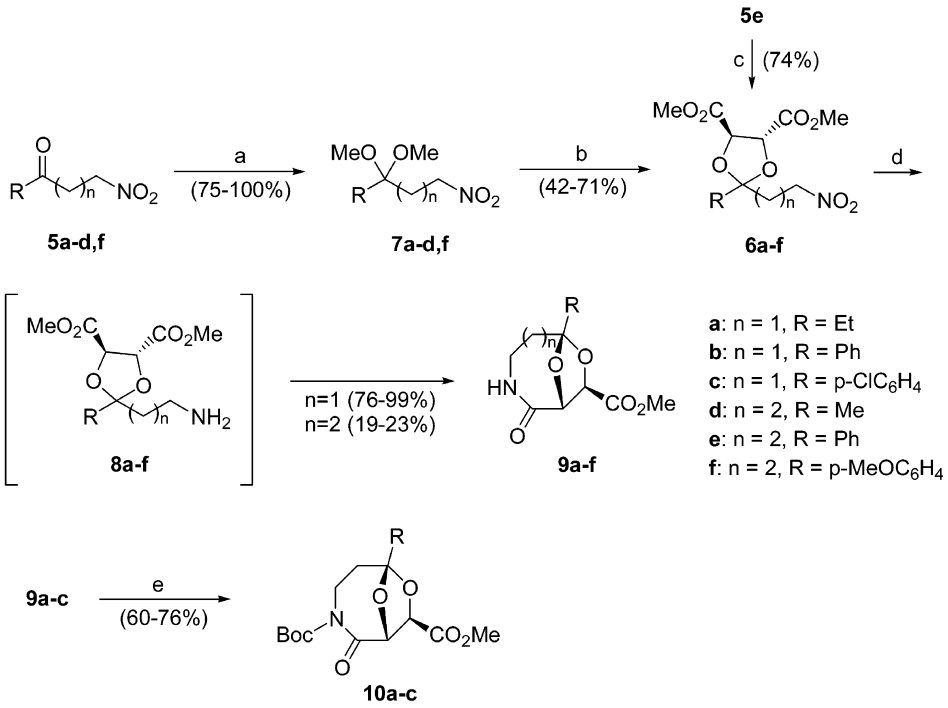
This proved to be the successful method to afford the target compounds and the final synthesis is reported in Scheme 3.

Ketones **5a**–**d** and **5f** were converted into their corresponding dimethyl ketals by treatment with an excess of trimethyl ortoformate in methanol under *p*-TsOH catalysis.[14] Depending on the substrate, the reaction was left 72 h at room temperature (**5a** and **5f**) or refluxed for 5 h (**5b**–**d**) affording **7a**–**d** and **7f** in very good yields (75% to quantitative). Apart from ketones **5b** and **5c**, conversions were always quantitative and the product recovered after the usual work-up could be used without further purification in the next step. *Trans*-ketalisations using dimethyl (*R*,*R*)-tartrate (**4a**) was performed under the conditions reported by Seebach et al.[15] for aromatic aldehydes. The use of 2 equiv. of $BF_3{\cdot}Et_2O$ in anhydrous ethyl acetate at 0 °C allowed the *trans*-ketalisation of **7a**–**d** and **7f** into **6a**–**d** and **6f**, yields ranging from 42 to 71% after purification. In all cases, starting β- or γ-nitroketones (20–30%) are re-formed during the reaction and they can be recovered by chromatographic purification, allowing material recycling when repeating the first step of the synthesis. Tartaric ketal **6e** was synthesised starting from γ-nitroketone **5e** under the conditions reported in Table 1 (entry 10).

Reduction of the nitro group to amino was obtained by hydrogenation on Raney-Ni of **7a**–**f** in methanol at room temperature in 16 h.[16] Surprisingly, in the case of substrates **7a**–**f**, we did not recover the corresponding amines **8a**–**f**, as we expected in analogy with the synthesis of **3**.[9] In our case, the amide formation that allows the ring closure is spontaneous during the reduction, so that cyclic 8-membered amides **9a**–**c** were obtained in good yields (76–99%) and high purity after filtration from the catalyst. On the other hand, in the case of substrates **7d**–**f**, cyclic 9-membered amides **9d**–**f** was obtained as main products, together with unidentified by-products. After chromatographic purification, pure **9d**–**f** were obtained in 19–24% yields and in the MeOH fraction we recovered a complex mixture of by-products, where amines **8d**–**f** were probably also present but could not be isolated.

Since compounds **9a**–**c** are more readily accessible, we decided to prepare their *N*-*tert*-butoxycarbonyl derivatives, as an example of amide protection that could be useful in the subsequent functional group transformation.

Amides **9a**–**c** were protected as *N*-Boc derivatives by



Scheme 3. (a) $HC(OMe)_3$, *p*-TsOH cat., MeOH, reflux or rt, 5 or 48 h; (b) **4a**, BF_3:Et_2O, EtOAc, 0 °C, 4 h; (c) **4b**, DCM, H_2SO_4 cat., rt, 48 h; (d) Raney-Ni, H_2, MeOH, rt, 16 h; (e) Boc_2O, Et_3N, DMAP cat., DCM, reflux, 18 h.

treatment in refluxing CH_2Cl_2 with Boc_2O and Et_3N in the presence of a catalytic amount of DMAP.[17] After 18 h, **10a–c** were recovered in fair yields (60–76%).

In this way we realised the synthesis of two new classes of BTKa, where the cyclic amide consists in a 8- or 9-membered ring and the substituent on the bridgehead carbon that derives from the ketone moiety is an aliphatic chain (**9a**, **9d**) or a phenyl group (**9b**, **9e**) or a *p*-substituted aromatic ring (**9c**, **9e**).

There are a few advantages in this approach: first, since the formation of the amide bond spontaneously occurs after the reduction of the nitro group, there is no need to use expensive peptide coupling reagents nor, in most cases, to purify the product; then, the isostere is obtained as the free amide that can be suitably protected, depending on the subsequent use of the substrate.

The aim of the present work was to obtain the ring enlargement of the rigid *exo* BTKa scaffolds and it also seemed interesting to evaluate how this modification would affect the conformational freedom of these compounds that represent a new class of dipeptide isosteres.

We, therefore, performed a complete conformational analysis on amides **9a**, **9b**, **9d** and **9e**.

As expected, these compounds are less rigid than their 7-membered counterparts and the 8-*exo* and 9-*exo* BTKa are more prone to take different conformations. Molecular modeling calculations revealed that the most interesting feature lies in the distance between the aromatic ring and the carbomethoxy group. This is found to decrease as the ring enlarges: in compounds **9b** and **9e**, the average distance is 3.4 and 3.0 Å, respectively, and it averages 3.8 Å in the 7-*exo* BTKa. This observation is confirmed by the experimental ^1H NMR data: the shielding effect of the aromatic ring increases and the OCH_3 group resonates at 3.75 (7-*exo* BTKa,[2] **2a**), 3.70 (8-*exo* BTKa, **9b**) and 3.37 ppm (9-*exo* BTKa, **9e**).

3. Conclusions

In this work, we prepared two classes of modified BTKa, where the ring size was increased from 7- up to 8- and 9-members.

As starting materials we used β- and γ-nitroketones. The synthesis presents the two key steps in reversed order with respect to the previously reported methodology: first the carbonyl is protected as ketal, and then the amide bond is formed. The presence of the nitro group seems to influence the reactivity of the carbonyl and the ketalisation using (*R*,*R*)-dimethyl tartaric ester as a partner diol was thus extensively studied, since the well known reaction conditions failed on these substrates. When tartaric ketals were obtained, the subsequent hydrogenation on Raney-Ni of the nitro group surprisingly afforded directly the 8-membered cyclic compounds, whereas in the case of 9-membered cyclic amides the reaction afforded a complex mixture of compounds, including the target lactames.

As expected by considering the ring dimensions, conformational analysis performed on these molecules revealed an increased flexibility with respect to 7-*exo* BTKa. However, an interesting feature of these compounds consists in the distance between the carbomethoxy group and the aromatic ring on the bridgehead carbon that decreases as the ring

enlarges. This explains the experimental upfield shift of the OCH_3 group observed in the ^1H NMR when passing from the 7-*exo* BTKa to the 8- and 9-*exo* ones. This structural characteristic could be useful in further applications.

4. Experimental

4.1. General

Melting points are uncorrected. Chromatographic separations were performed under pressure on silica gel by flash-column techniques; R_f values refer to TLC carried out on 25-mm silica gel plates (Merck F254), with the same eluent as indicated for the column chromatography. IR spectra were recorded with a Perkin–Elmer 881 spectrophotometer in $CHCl_3$ solution. ^1H NMR (200 MHz) and ^{13}C NMR (50.33 MHz) spectra were recorded with a Varian XL 200 instrument in $CDCl_3$ solution. Mass spectra were carried out by EI at 70 eV, unless otherwise stated, on 5790A–5970A Hewlett–Packard and QMD 1000 Carlo Erba instruments. Microanalyses were carried out with a Perkin–Elmer 2400/2 elemental analyser. Optical rotations were determined with a JASCO DIP-370 instrument. Molecular modeling was carried out by using the MM2* force field implemented in MacroModel v6.5 using the default values of the software for all calculations. (4*R*,5*R*)-2-Methoxy-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester **4b**,[18] β-nitroketone **5a**,[19] and γ-nitroketones **5d–f**[16] were synthesised as reported.

4.1.1. 1-Phenyl-3-nitro-1-propanone (5b). Synthesised as reported for **5a**,[19] starting from 1-phenylpropenone (2.10 g, 15.9 mmol). After chromatografic purification (eluent: CH_2Cl_2–petroleum ether, 1:1, R_f=0.13), pure **5b** (1.37 g, 48%) was obtained as white solid.

Compound **5b**. Mp 77–78 °C. ^1H NMR δ (ppm): 7.99–7.95 (m, 2H), 7.65–7.45 (m, 3H), 4.82 (t, *J*=6.2 Hz, 2H), 3.65 (t, *J*=6.2 Hz, 2H). ^{13}C NMR δ (ppm): 195.4 (s), 138.6 (s), 129.4 (d), 129.3 (d, 2C), 128.7 (d, 2C), 69.8 (t), 35.4 (t). MS *m*/*z* (%): 105 ($M^+-(CH_2)_2NO_2$, 100), 77 (65). IR ($CDCl_3$): 1708, 1689, 1555 and 1364 cm^{-1}. Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.52; H, 5.05; N, 7.58.

4.1.2. 1-(4-Chlorophenyl)-3-nitro-1-propanone (5c). Synthesised as reported,[20] starting from 3-chloro-1-(4-chlorophenyl)-1-propanone (2.00 g, 9.85 mmol). After crystallisation from hexane, pure **5c** (1.68 g, 80%) was obtained as pale yellow solid.

Compound **5c**. Mp 71–72 °C (lit.[20b] 79–80 °C). ^1H NMR δ (ppm): 7.91 (d, *J*=8.4 Hz, 2H), 7.47 (d, *J*=8.4 Hz, 2H), 4.82 (t, *J*=5.8 Hz, 2H), 3.62 (t, *J*=5.8 Hz, 2H). ^{13}C NMR δ (ppm): 193.8 (s), 140.3 (s), 133.8 (s), 129.4 (d, 2C), 129.0 (d, 2C), 69.0 (t), 34.7 (t). MS *m*/*z* (%): 213 (M^+, 1), 167 (M^+-NO_2, 18), 139 ($M^+-(CH_2)_2NO_2$, 100). IR ($CDCl_3$): 1691, 1560, 1374 cm^{-1}.

4.1.3. 3,3-Dimethoxy-1-nitro-pentane (7a). To a solution of **5a** (686 mg, 5.23 mmol) in MeOH (8 mL), trimethyl ortoformate (8 mL) and a catalytic amount of *p*-TsOH were added. The solution was left under magnetic stirring at room temperature. After 72 h, satd $NaHCO_3$ was added (10 mL), the product extracted with CH_2Cl_2 (3×10 mL) and the organic layer dried over Na_2SO_4. After filtration and evaporation of the solvent, crude **7a** was obtained in quantitative yield and used in the next step without further purification.

Compound **7a**. ^1H NMR δ (ppm): 4.34 (m, 2H, CH_2NO_2), 3.15 (s, 6H, OCH_3), 2.33 (m, 2H, $CH_2CH_2NO_2$), 1.56 (q, *J*=7.7 Hz, 2H, CH_2CH_3), 0.86 (t, *J*=7.7 Hz, 3H, CH_3). ^{13}C NMR δ (ppm): 101.6 (s), 71.5 (t), 48.0 (q, 2C), 29.8 (t), 25.9 (t), 7.9 (q). MS *m*/*z* (%): 178 (M^++1, 1.2), 113 ($M^+-(CH_2)_2NO_2$, 10), 103 (53), 71 (57), 57 (100).

4.1.4. (1,1-Dimethoxy-3-nitro-propyl)-benzene (7b). Prepared as described for **7a**, starting from **5b** (506 mg, 2.83 mmol) but refluxing the solution for 5 h. Crude **7b**, isolated after the work up in 80% yield, was used in the next step without further purification.

Compound **7b**. ^1H NMR δ (ppm): 7.39–7.22 (m, 5H, Ph), 4.00 (m, 2H, CH_2NO_2), 3.12 (s, 6H, OCH_3), 2.57 (m, 2H, $CH_2CH_2NO_2$). ^{13}C NMR δ (ppm): 138.8 (s), 128.8 (d), 128.4 (d, 2C), 126.5 (d, 2C), 101.4 (s), 71.3 (t), 48.9 (q, 2C), 34.6 (t). MS *m*/*z* (%): 225 (M^+, 1), 178 (8), 151 (21), 105 (100), 77 (54).

4.1.5. 1-Chloro-4-(1,1-dimethoxy-3-nitro-propyl)-benzene (7c). Prepared as described for **7a**, starting from **5c** (285 mg, 1.33 mmol) but refluxing the solution for 5 h. Crude **7c**, isolated after the work up in 75% yield, was used in the next step without further purification.

Compound **7c**. ^1H NMR δ (ppm): 7.34–7.26 (m, 4H, C_6H_4), 3.97 (m, 2H, CH_2NO_2), 3.08 (s, 6H, OCH_3), 2.54 (m, 2H, $CH_2CH_2NO_2$). ^{13}C NMR δ (ppm): 144.8 (s), 137.5 (s), 128.6 (d, 2C), 128.1 (d, 2C), 101.1 (s), 71.1 (t), 48.9 (q, 2C), 34.5 (t). MS (30 eV) *m*/*z* (%): 185 ($M^+-(CH_2)_2NO_2$, 19), 139 (100).

4.1.6. 4,4-Dimethoxy-1-nitro-pentane (7d). Prepared as described for **7a**, starting from **5d** (651 mg, 4.96 mmol) but refluxing the solution for 5 h. Crude **7d**, isolated after the work up in quantitative yield, was used in the next step without further purification.

Compound **7d**. ^1H NMR δ (ppm): 4.38 (t, *J*=7.0 Hz, 2H, CH_2NO_2), 3.15 (s, 6H, OCH_3), 2.14–1.96 (m, 2H, $CH_2CH_2CH_2NO_2$), 1.70–1.61 (m, 2H, $CH_2CH_2CH_2NO_2$), 1.27 (s, 3H, CH_3). ^{13}C NMR δ (ppm): 100.6 (s), 75.2 (d), 47.7 (q, 2C), 32.8 (t), 22.2 (t), 20.5 (q). MS *m*/*z* (%) 177 (M^+, 1), 89 ($M^+-(CH_2)_3NO_2$, 100).

4.1.7. 1-(1,1-Dimethoxy-3-nitro-butyl)-4-methoxy-benzene (7f). Prepared as described for **7a**, starting from **5f** (1.01 g, 4.53 mmol). Crude **7f**, isolated after the work up in quantitative yield, was used in the next step without further purification.

Compound **7f**. ^1H NMR δ (ppm): 7.34 (d, *J*=8.8 Hz, 2H, Ph), 6.86 (d, *J*=8.8 Hz, 2H, Ph), 4.17 (t, *J*=7.0 Hz, 2H, CH_2NO_2), 3.80 (s, 3H, $C_6H_4OCH_3$), 3.12 (s, 6H, OCH_3),

1.96–1.90 (m, 2H, $CH_2CH_2CH_2NO_2$), 1.89–1.63 (m, 2H, $CH_2CH_2CH_2NO_2$). ^{13}C NMR δ (ppm): 159.2 (s), 131.9 (s), 127.9 (d, 2C), 113.4 (d, 2C), 102.7 (s), 75.1 (t), 55.2 (q), 48.6 (q, 2C), 33.7 (t), 21.8 (t). MS *m/z* (%) 181 ($M^+-(CH_2)_3NO_2$, 73), 135 (100).

4.1.8. (4*R*,5*R*)-2-Ethyl-2-(2-nitro-ethyl)-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester (6a). To a solution of **7a** (927 mg, 5.23 mmol) and (*R*,*R*)-dimethyl tartrate **4a** (1.86 g, 10.46 mmol) in anhydrous EtOAc (10 mL), cooled at 0 °C, BF_3:Et_2O (2 equiv., 1.23 mL) was added. After 4 h, the solution was diluted with EtOAc (10 mL) and $NaHCO_3$ satd (10 mL) added; the resulting mixture was left under vigorous stirring for 10 min. After separation of the phases, the organic layer was dried over Na_2SO_4. After filtration and evaporation of the solvent, crude **6a** was obtained and purification by chromatography (eluent: EtOAc–petroleum ether, 1:3, R_f=0.20) afforded pure **6a** (637 mg, 42%) as colourless oil.

Compound **6a**. $[\alpha]_D^{25}=-12.1$ (*c* 0.3, $CHCl_3$). ^{1}H NMR δ (ppm): 4.78 (d, *J*=6.2 Hz, 1H, C*H*CO_2Me), 4.64 (d, *J*=6.2 Hz, 1H, C*H*CO_2Me), 4.57–4.48 (m, 2H, CH_2NO_2), 3.83 (s, 3H, CO_2CH_3), 3.80 (s, 3H, CO_2CH_3), 2.54–2.45 (m, 2H, $CH_2CH_2NO_2$), 1.70 (q, *J*=7.4 Hz, 2H, CH_2CH_3), 0.96 (t, *J*=7.4 Hz, 3H, CH_2CH_3). ^{13}C NMR δ (ppm): 169.5 (s), 169.2 (s), 115.2 (s), 77.5 (d), 76.9 (d), 70.3 (t), 52.9 (q, 2C), 33.1 (t), 30.6 (t), 7.9 (q). MS *m/z* (%) 291 (M^+, 0.12), 244 (1), 217 (48), 215 (84), 55 (100). IR ($CHCl_3$) 1751, 1557 and 1383, 1439 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO_8$: C, 45.36; H, 5.88; N, 4.81. Found: C, 45.81; H, 6.05; N, 4.25.

4.1.9. (4*R*,5*R*)-2-(2-Nitro-ethyl)-2-phenyl-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester (6b). Prepared as described for **6a**, starting from **7b** (630 mg, 2.83 mmol) and obtaining **6b** (600 mg, 63%) after chromatographic purification (eluent: EtOAc–petroleum ether, 1:4, R_f=0.19) as yellow oil.

Compound **6b**. $[\alpha]_D^{25}=+7.91$ (*c* 0.6, $CHCl_3$). ^{1}H NMR δ (ppm): 7.48–7.42 (m, 2H, Ph), 7.36–7.28 (m, 3H, Ph), 4.87 (d, *J*=5.1 Hz, 1H, C*H*CO_2Me), 4.73 (d, *J*=5.1 Hz, 1H, C*H*CO_2Me), 4.69–4.47 (m, 2H, CH_2NO_2), 3.84 (s, 3H, CO_2CH_3), 3.47 (s, 3H, CO_2CH_3), 2.86–2.57 (m, 2H, $CH_2CH_2NO_2$). ^{13}C NMR δ (ppm): 168.9 (s), 168.7 (s), 139.1 (s), 129.2 (d), 128.2 (d, 2C), 125.6 (d, 2C), 112.4 (s), 77.5 (d), 76.1 (d), 70.1 (t), 52.9 (q), 52.4 (q), 37.2 (t). MS *m/z* (%) 292 (M^+-HNO_2, 0.6), 265 (100), 232 (6), 155 (1), 105 (27), 77 (14). IR ($CHCl_3$) 1752, 1557 and 1383, 1439 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_8$: C, 53.10; H, 5.05; N, 4.13. Found: C, 53.24; H, 5.08; N, 4.30.

4.1.10. (4*R*,5*R*)-2-(4-Chloro-phenyl)-2-(2-nitro-ethyl)-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester (6c). Prepared as described for **6a**, starting from **7c** (276 mg, 1.06 mmol) and obtaining **6c** (175 mg, 44%) after chromatographic purification (eluent: CH_2Cl_2, R_f=0.38) as dark yellow oil.

Compound **6c**. $[\alpha]_D^{25}=+12.4$ (*c* 0.1, $CHCl_3$). ^{1}H NMR δ (ppm): 7.35 (d, *J*=8.6 Hz, 2H, Ph), 7.24 (d, *J*=8.6 Hz, 2H, Ph), 4.76 (d, *J*=5.5 Hz, 1H, C*H*CO_2Me), 4.67 (d, *J*=5.5 Hz, 1H, C*H*CO_2Me), 4.64–4.39 (m, 2H, CH_2NO_2), 3.77 (s, 3H, CO_2CH_3), 3.45 (s, 3H, CO_2CH_3), 2.75–2.47 (m, 2H, $CH_2CH_2NO_2$). ^{13}C NMR δ (ppm): 168.5 (s), 168.4 (s), 137.8 (s), 135.1 (s), 128.4 (d, 2C), 127.1 (d, 2C), 112.0 (s), 77.6 (d), 76.2 (d), 70.0 (t), 53.0 (q), 52.5 (q), 37.2 (t). MS *m/z* (%): 299 ($M^+-(CH_2)_2NO_2$, 95), 139 (100), 111 (40). IR ($CDCl_3$): 3151, 1601, 1560 and 1381 cm^{-1}. Anal. Calcd for $C_{15}H_{16}ClNO_8$: C, 48.20; H, 4.32; N, 3.75. Found: C, 48.60; H, 4.49; N, 3.69.

4.1.11. (4*R*,5*R*)-2-Methyl-2-(3-nitro-propyl)-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester (6d). Prepared as described for **6a**, starting from **7d** (400 mg, 2.25 mmol) and obtaining **6d** (467 mg, 71%) after chromatographic purification (eluent: EtOAc–petroleum ether, 1:3, R_f=0.26) as colourless oil.

Compound **6d**. $[\alpha]_D^{25}=-23.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR δ (ppm): 4.80 (d, *J*=5.9 Hz, 1H, C*H*CO_2Me), 4.69 (d, *J*=5.9 Hz, 1H, C*H*CO_2Me), 4.43 (t, *J*=7.3 Hz, 2H, CH_2NO_2), 3.80 (s, 6H, CO_2CH_3), 2.23–2.12 (m, 2H, $CH_2CH_2CH_2NO_2$), 1.87–1.79 (m, 2H, $CH_2CH_2CH_2NO_2$), 1.42 (s, 3H, CH_3). ^{13}C NMR δ (ppm): 169.8 (s), 169.4 (s), 114.5 (s), 77.4 (d), 76.9 (d), 75.3 (t), 52.9 (q, 2C), 35.6 (t), 24.5 (q), 21.8 (t). MS *m/z* (%): 276 (M^+-CH_3, 20), 232 (M^+-CO_2Me, 6), 203 ($M^+-(CH_2)_3NO_2$, 100). IR ($CDCl_3$): 1755, 1554 and 1383 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO_8$: C, 45.36; H, 5.88; N, 4.81. Found: C, 45.40; H, 5.89; N, 4.44.

4.1.12. (4*R*,5*R*)-2-(2-Nitro-propyl)-2-phenyl-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester (6e). To a solution of **5e** (100 mg, 0.52 mmol) and **4b** (150 mg, 0.68 mmol) in CH_2Cl_2 (2 mL), H_2SO_4 (50 μL) is added. After 48 h solvent is removed and 10% $NaHCO_3$ solution (5 mL) is added and the product extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried on Na_2SO_4 and filtration and evaporation of the solvent afforded crude **6e**. This was purified by flash chromatography (eluent: EtOAc–petroleum ether, 1:3, R_f=0.24), obtaining pure **6e** (135 mg, 74%) as yellow oil.

Compound **6e**. $[\alpha]_D^{25}=+13.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR δ (ppm): 7.46–7.41 (m, 2H, Ph), 7.34–7.29 (m, 3H, Ph), 4.87 (d, *J*=5.4 Hz, 1H, C*H*CO_2Me), 4.76 (d, *J*=5.4 Hz, 1H, C*H*CO_2Me), 4.48–4.41 (m, 2H, CH_2NO_2), 3.83 (s, 3H, CO_2CH_3), 3.49 (s, 3H, CO_2CH_3), 2.21–2.00 (m, 4H, $CH_2CH_2CH_2NO_2$). ^{13}C NMR δ (ppm): 162.9 (s), 169.0 (s), 139.8 (s), 128.8 (d), 128.1 (d, 2C), 125.7 (d, 2C), 113.9 (s), 77.4 (d), 76.1 (d), 75.1 (t), 52.9 (q), 52.4 (q), 36.8 (t), 21.4 (t). MS *m/z* (%): 265 ($M^+-(CH_2)_3NO_2$, 100), 105 (25), 77 (11). IR ($CHCl_3$): 1751, 1554 and 1371, 1438 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_8$: C, 54.39; H, 5.42; N, 3.96. Found: C, 54.34; H, 5.56; N, 4.27.

4.1.13. (4*R*,5*R*)-2-(4-Methoxy-phenyl)-2-(2-nitro-propyl)-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester (6f). Prepared as described for **6a**, starting from **7f** (500 mg, 1.85 mmol) and obtaining **6f** (285 mg, 45%) after chromatographic purification (eluent: EtOAc–petroleum ether, 1:3, R_f=0.25) as colourless oil.

Compound **6f**. $[\alpha]_D^{25}=+12.1$ (*c* 0.3, $CHCl_3$). ^{1}H NMR δ (ppm): 7.35 (d, *J*=8.8 Hz, 2H, Ph), 6.82 (d, *J*=8.8 Hz, 2H, Ph), 4.85 (d, *J*=5.5 Hz, 1H, C*H*CO_2Me), 4.73 (d, *J*=5.5 Hz,

1H, C*H*CO_2Me), 4.44–4.40 (m, 2H, CH_2NO_2), 3.82 (s, 3H, CO_2CH_3), 3.77 (s, 3H, OCH_3), 3.52 (s, 3H, CO_2CH_3), 2.17–2.02 (m, 4H, $CH_2CH_2CH_2NO_2$). ^{13}C NMR δ (ppm): 169.0 (s), 168.8 (s), 159.6 (s), 131.7 (s), 126.9 (d, 2C), 113.7 (s), 113.2 (d, 2C), 77.2 (d), 75.9 (d), 75.0 (t), 55.0 (q), 52.6 (q), 52.2 (q), 36.8 (t), 21.4 (t). MS *m/z* (%) 295 ($M^+-(CH_2)_3NO_2$, 100), 135 (79), 107 (6). IR ($CDCl_3$): 1751, 1553 and 1372 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_9$: C, 53.26; H, 5.52; N, 3.65. Found: C, 53.38; H, 5.49; N, 3.58.

4.1.14. (1*R*,6*S*,8*R*)-6-Ethyl-2-oxo-7,9-dioxa-3-aza-bicyclo-[4.2.1]nonane-8-carboxylic acid methyl ester (9a). A solution of **7a** (637 mg, 2.19 mmol) in MeOH (20 mL) was added under stirring to a prehydrogenated suspension of wet Raney-Ni (924 mg, washed three times with 5 mL of MeOH before the addition of the solution of **7a**) in the same solvent (10 mL). The mixture was left under hydrogen atmosphere for 16 h at room temperature and then filtered twice on a Celite layer and finally evaporated to give pure **9a** (491 mg, 99%) as pale yellow solid.

Compound **9a**. Mp 66–67 °C. $[\alpha]_D^{25}=-75.6$ (*c* 0.8, $CHCl_3$). ^{1}H NMR δ (ppm): 6.26 (s br, 1H, N*H*), 4.90 (br s, 1H, C*H*$CHCO_2CH_3$), 4.76 (d, *J*=1.8 Hz, 1H, C*H*CO_2CH_3), 3.78 (s, 3H, CO_2CH_3), 3.33–3.25 (m, 2H, CH_2NHC=O), 2.08–2.02 (m, 2H, CH_2CH_2NHC=O), 1.88 (q, *J*=7.4 Hz, 2H, CH_2CH_3), 0.99 (t, *J*=7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR δ (ppm): 174.9 (s), 169.8 (s), 115.2 (s), 81.6 (d), 77.1 (d), 52.6 (q), 38.6 (t), 37.5 (t), 32.0 (t), 7.4 (q). MS *m/z* (%) 229 (M^+, 17), 170 (40), 113 (79), 97 (80), 56 (100). IR ($CHCl_3$) 3405, 1760, 1671, 1357 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.63; H, 6.46; N, 5.99.

4.1.15. (1*R*,6*R*,8*R*)-2-Oxo-6-phenyl-7,9-dioxa-3-aza-bicyclo[4.2.1]nonane-8-carboxylic acid methyl ester (9b). Prepared as described for **9a**, starting from **7b** (400 mg, 1.18 mmol) and obtaining pure **9b** (279 mg, 85%) as pale yellow solid.

Compound **9b**. Mp 95–96 °C. $[\alpha]_D^{25}=-32.8$ (*c* 0.5, $CHCl_3$). ^{1}H NMR δ (ppm): 7.63–7.58 (m, 2H, Ph), 7.43–7.29 (m, 3H, Ph), 6.30 (br s, 1H, N*H*), 5.05 (s, 1H, C*H*$CHCO_2CH_3$), 4.95 (d, *J*=2.2 Hz, 1H, C*H*CO_2CH_3), 3.70 (s, 3H, CO_2CH_3), 3.51–3.42 (m, 2H, CH_2NHC=O), 2.42–2.33 (m, 2H, CH_2CH_2NHC=O). ^{13}C NMR δ (ppm): 174.8 (s), 169.5 (s), 140.6 (s), 128.6 (d), 128.2 (d, 2C), 124.8 (d, 2C), 113.7 (s), 82.0 (d), 77.3 (d), 52.6 (q), 40.9 (t), 37.5 (t). MS *m/z* (%) 277 (M^+, 2), 218 (22), 147 (26), 104 (100), 77 (92). IR ($CHCl_3$) 3405, 1761, 1710, 1673 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C: 60.21; H, 5.56; N, 4.61.

4.1.16. (1*R*,6*R*,8*R*)-6-(4-Chloro-phenyl)-2-oxo-7,9-dioxa-3-aza-bicyclo[4.2.1]nonane-8-carboxylic acid methyl ester (9c). Prepared as described for **9a**, starting from **7c** (150 mg, 0.40 mmol) and obtaining pure **9c** (95 mg, 76%) as yellow oil.

Compound **9c**. $[\alpha]_D^{25}=-23.6$ (*c* 0.3, $CHCl_3$). ^{1}H NMR δ (ppm): 7.54 (d, *J*=8.4 Hz, 2H, Ph), 7.33 (d, *J*=8.4 Hz, 2H, Ph), 6.75 (br s, 1H, N*H*), 5.01 (s, 1H, C*H*$CHCO_2CH_3$), 4.94 (br s, 1H, C*H*CO_2CH_3), 3.69 (s, 3H, CO_2CH_3), 3.52–3.34 (m, 2H, CH_2NHC=O), 2.40–2.22 (m, 2H, CH_2CH_2-NHC=O). ^{13}C NMR δ (ppm): 174.4 (s), 169.3 (s), 139.2 (s), 134.6 (s), 128.3 (d, 2C), 126.3 (d, 2C), 113.2 (s), 82.0 (d), 77.4 (d), 52.7 (q), 41.1 (t), 37.6 (t). MS *m/z* (%) 252 (M^+-CO_2Me, 19), 139 (100), 111 (46). IR ($CDCl_3$): 1763, 1674 cm^{-1}. Anal. Calcd for $C_{14}H_{14}ClNO_5\cdot H_2O$: C, 50.10; H, 4.89; N, 4.25. Found: C: 50.00; H, 4.69; N, 4.19.

4.1.17. (1*R*,7*S*,9*R*)-7-Methyl-2-oxo-8,10-dioxa-3-aza-bicyclo[5.2.1]decane-9-carboxylic acid methyl ester (9d). Prepared as described for **9a**, starting from **7d** (445 mg, 1.53 mmol) and obtaining crude **9d**. After chromatografic purification (eluent: EtOAc–petroleum ether, 3:1, R_f=0.36) pure **9d** (68 mg, 19%) as white solid.

Compound **9d**. Mp 149–150 °C. $[\alpha]_D^{25}=-69.8$ (*c* 0.2, $CHCl_3$). ^{1}H NMR δ (ppm): 6.53 (br s, 1H, N*H*), 5.00 (d, *J*=2.6 Hz, 1H, C*H*$CHCO_2CH_3$), 4.86 (d, *J*=2.6 Hz, 1H, C*H*CO_2CH_3), 4.12–3.95 (m, 1H, CH_aH_bNHC=O), 3.79 (s, 3H, CO_2CH_3), 3.20–3.04 (m, 1H, CH_aH_bNHC=O), 1.89–1.67 (m, 4H, $CH_2CH_2CH_2$NHC=O), 1.51 (s, 3H, CH_3). ^{13}C NMR δ (ppm): 174.2 (s), 170.5 (s), 115.1 (s), 79.3 (d), 78.9 (d), 52.8 (q), 41.1 (t), 33.6 (t), 25.1 (t), 24.8 (q). IR ($CDCl_3$): 1751, 1653 cm^{-1}. MS (30 eV) *m/z* (%): 230 (M^++1, 11), 214 (M^+-CH_3, 3), 187 (51), 84 (100). Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C: 52.23; H, 6.43; N, 5.95.

4.1.18. (1*R*,7*R*,9*R*)-2-Oxo-7-phenyl-8,10-dioxa-3-aza-bicyclo[5.2.1]decane-9-carboxylic acid methyl ester (9e). Prepared as described for **9a**, starting from **7e** (90 mg, 0.26 mmol) and obtaining crude **9e**. After chromatografic purification (eluent: EtOAc–petroleum ether, 1:3, 1% Et_3N, R_f=0.16) pure **9e** (17 mg, 24%) as yellow oil.

Compound **9e**. $[\alpha]_D^{25}=-32.8$ (*c*0.5, $CHCl_3$). ^{1}H NMR δ (ppm): 7.51–7.46 (m, 2H, Ph), 7.40–7.27 (m, 3H, Ph), 6.35 (br s, 1H, N*H*), 5.31 (d, *J*=1.8 Hz, 1H, C*H*$CHCO_2CH_3$), 4.93 (d, *J*=1.8 Hz, 1H, C*H*CO_2CH_3), 4.15–4.07 (m, 1H, CH_aH_bNHC=O), 3.37 (s, 3H, CO_2CH_3), 3.25–3.16 (m, 1H, CH_aH_bNHC=O), 2.24–1.82 (m, 4H, $CH_2CH_2CH_2$-NHC=O). ^{13}C NMR δ (ppm): 173.8 (s), 169.3 (s), 141.5 (s), 128.3 (d), 127.8 (d, 2C), 125.3 (d, 2C), 114.7 (s), 79.6 (d), 78.8 (d), 52.3 (q), 42.2 (t), 36.7 (t), 25.8 (t). MS *m/z* (%): 291 (M^+, 2), 105 (24), 104 (100). IR ($CDCl_3$): 3400, 1745, 1655 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 60.62; H, 5.92; N, 4.76.

4.1.19. (1*R*,7*R*,9*R*)-7-(4-Methoxy-phenyl)-2-oxo-8,10-dioxa-3-aza-bicyclo[5.2.1]decane-9-carboxylic acid methyl ester (9f). Prepared as described for **9a**, starting from **7f** (150 mg, 0.39 mmol) and obtaining crude **9f**. After chromatografic purification (eluent: EtOAc, R_f=0.52) pure **9f** (29 mg, 23%) as yellowish solid.

Compound **9f**. Mp 124–125 °C. $[\alpha]_D^{25}=-25.7$ (*c*0.3, $CHCl_3$). ^{1}H NMR δ (ppm): 7.41 (d, *J*=8.8 Hz, 2H, Ph), 6.83 (d, *J*=8.8 Hz, 2H, Ph), 6.58 (br s, 1H, N*H*), 5.28 (d, *J*=1.5 Hz, 1H, C*H*$CHCO_2CH_3$), 4.91 (d, *J*=1.5 Hz, 1H, C*H*CO_2CH_3), 4.13–4.03 (m, 1H, CH_aH_bNHC=O), 3.78 (s, 3H, OCH_3), 3.43 (s, 3H, CO_2CH_3), 3.27–3.13 (m, 1H, CH_aH_bNHC=O), 2.22–1.86 (m, 4H, $CH_2CH_2CH_2$-NHC=O). ^{13}C NMR δ (ppm): 173.9 (s), 169.3 (s), 159.5 (s), 133.5 (s), 126.7 (d, 2C), 114.7 (s), 113.1 (d, 2C), 79.5

(d), 78.7 (d), 55.2 (q), 52.4 (q), 42.1 (t), 36.3 (t), 25.8 (t). MS *m/z* (%): 321 (M^+, 3), 262 (13), 177 (19), 135 (100). IR ($CDCl_3$): 1747, 1653 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_6 \cdot H_2O$: C, 56.63; H, 6.24; N, 4.13. Found: C, 57.09; H, 6.08; N, 3.93.

4.1.20. (1*R*,6*S*,8*R*)-6-Ethyl-2-oxo-7,9-dioxa-3-aza-bicyclo-[4.2.1]nonane-3,8-dicarboxylic acid 3-*tert*-butyl ester 8-methyl ester (10a). To a solution of **9a** (350 mg, 1.55 mmol) in anhydrous CH_2Cl_2 (10 mL) Boc_2O (690 mg, 3.10 mmol), Et_3N (325 μL, 2.32 mmol) and catalytic DMAP (18 mg, 0.16 mmol) were added under nitrogen atmosphere. The resulting solution was refluxed for 6 h; a second portion of Boc_2O (690 mg, 3.10 mmol) was added after this period and the mixture refluxed for further 16 h. After cooling to rt, H_2O (10 mL) was added and the phases separated. The organic layer was washed with 5% $KHSO_4$ (2×10 mL), satd $NaHCO_3$ (2×10 mL), brine (2×10 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, crude **10a** was obtained. Chromatographic purification (eluent: petroleum ether–EtOAc, 6:1, R_f=0.33) afforded pure **10a** (388 mg, 76%) as yellow oil.

Compound **10a**. $[\alpha]_D^{25}=-47.8$ (*c*1.0, $CHCl_3$). ^1H NMR (1.6:1 mixture of rotamers) δ (ppm): 4.92 (d, *J*=2.2 Hz, 1H major rotamer, C*H*CO_2Me), 4.71 (d, *J*=2.2 Hz, 1H minor rotamer, C*H*CO_2Me), 4.69 (bs s, 1H minor rotamer, C*H*$CHCO_2$Me), 4.48 (br s, 1H major rotamer, C*H*$CHCO_2$-Me), 4.12 (dt, *J*=15.8, 4.0 Hz, 1H major rotamer, CH_aH_bN), 3.71 (s, 3H major rotamer, CO_2CH_3), 3.70 (s, 3H minor rotamer, CO_2CH_3), 3.70–3.64 (m, 1H minor rotamer, CH_aH_bN), 3.41–3.04 (m, 1H, CH_aH_bN), 2.05–1.82 (m, 2H, CH_2CH_2N), 1.77 (q, *J*=7.3 Hz, 2H, major rotamer, CH_2CH_3), 1.60 (q, *J*=7.3 Hz, 2H minor rotamer, CH_2CH_3), 1.39 (s, 9H major rotamer, *t*-Bu), 1.38 (s, 9H minor rotamer, *t*-Bu), 0.89 (t, *J*=7.3 Hz, 3H major rotamer, CH_2CH_3), 0.83 (t, *J*=7.3 Hz, 3H minor rotamer, CH_2CH_3). ^{13}C NMR δ (ppm): 174.0 and 169.4 (s), 169.8 and 168.1 (s), 116.9 and 116.3 (s), 83.4 and 83.1 (s), 82.5 and 77.6 (d), 77.4 and 76.9 (d), 52.7 and 52.6 (q), 39.2 and 37.2 (t), 35.6 and 35.4 (t), 31.3 and 30.5 (t), 28.4 and 27.9 (q, 3C), 7.9 and 7.4 (q). MS *m/z* (%): 228 (M^+−Boc, 7), 203 (95), 201 (32). IR ($CDCl_3$): 1753, 1711 cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_7$: C, 54.70; H, 7.04; N, 4.25. Found: C: 54.57; H, 7.24; N, 4.18.

4.1.21. (1*R*,6*R*,8*R*)-2-Oxo-6-phenyl-7,9-dioxa-3-aza-bicyclo[4.2.1]nonane-3,8-dicarboxylic acid 3-*tert*-butyl ester 8-methyl ester (10b). Prepared as described for **10a**, starting from **9b** (200 mg, 0.72 mmol) and obtaining, after chromatographic purification (eluent: petroleum ether–EtOAc, 6:1, R_f=0.38) pure **10b** (163 mg, 60%) as yellow oil.

Compound **10b**. $[\alpha]_D^{25}=-114.2$ (*c*0.5, $CHCl_3$). ^1H NMR δ (ppm): 7.63–7.58 (m, 2H, Ph), 7.40–7.30 (m, 3H, Ph), 5.17 (d, *J*=2.2 Hz, 1H, C*H*$CHCO_2CH_3$), 4.96 (d, *J*=2.2 Hz, 1H, C*H*CO_2CH_3), 4.36 (dt, *J*=15.8, 4.0 Hz, 1H, CH_aH_bN), 3.72 (s, 3H, CO_2CH_3), 3.53–3.40 (m, 1H, CH_aH_bN), 2.49–2.32 (m, 1H, C$H_aH_bCH_2$N), 2.26–2.12 (m, 1H, $CH_aH_bCH_2$N), 1.51 (s, 9H, Boc). ^{13}C NMR δ (ppm): 174.0 (s), 169.1 (s), 153.0 (s), 139.6 (s), 128.8 (d), 128.2 (d, 2C), 124.9 (d, 2C), 114.8 (s), 83.6 (s), 82.8 (d), 77.9 (d), 52.8 (q), 39.9 (t), 39.3 (t), 28.0 (q, 3C). MS *m/z* (%): 320 (M^+−*t*Bu, 1), 279 (M^+−Boc, 4), 105 (100). IR ($CDCl_3$): 1763, 1718 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C: 60.28; H, 6.00; N, 3.53.

4.1.22. (1*R*,6*R*,8*R*)-6-(4-Chloro-phenyl)-2-oxo-7,9-dioxa-3-aza-bicyclo[4.2.1]nonane-3,8-dicarboxylic acid 3-*tert*-butyl ester 8-methyl ester (10c). Prepared as described for **10a**, starting from **9c** (90 mg, 0.29 mmol) and obtaining, after chromatographic purification (eluent: petroleum ether–EtOAc, 7:1, R_f=0.23) pure **10c** (88 mg, 74%) as yellow oil.

Compound **10c**. $[\alpha]_D^{25}=-102.5$ (*c*0.8, $CHCl_3$). ^1H NMR δ (ppm): 7.44 (d, *J*=8.6 Hz, 2H, Ph), 7.31 (d, *J*=8.6 Hz, 2H, Ph), 5.15 (d, *J*=2.2 Hz, 1H, C*H*$CHCO_2CH_3$), 4.95 (d, *J*=2.2 Hz, 1H, C*H*CO_2CH_3), 4.43–4.27 (m, 1H, CH_aH_bN), 3.73 (s, 3H, CO_2CH_3), 3.55–3.38 (m, 1H, CH_aH_bN), 2.32–2.18 (m, 2H, CH_2CH_2N), 1.51 (s, 9H, Boc). ^{13}C NMR δ (ppm): 173.8 (s), 169.1 (s), 153.0 (s), 138.9 (s), 134.7 (s), 128.4 (d, 2C), 126.6 (d, 2C), 114.4 (s), 83.3 (s), 82.9 (d), 78.0 (d), 52.9 (q), 39.9 (t), 39.2 (t), 28.0 (q, 3C). MS (30 eV) *m/z* (%): 358 (M^+−*t*Bu, 3), 314 (M^+−Boc, 2), 254 (7), 139 (94), 57 (100). IR ($CDCl_3$): 1744, 1718 cm^{-1}. Anal. Calcd for $C_9H_{22}ClNO_7$: C, 55.41; H, 5.38; N, 3.40. Found: C: 55.59; H, 5.22; N, 3.19.

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