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Microwave-assisted multicomponent diastereoselective 1,3-dipolar cycloaddition of ethyl glyoxylate derived azomethine ylides†‡

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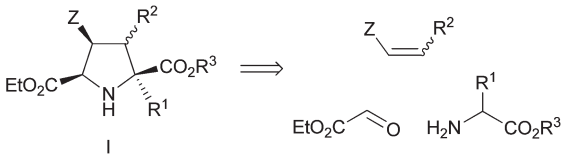
The thermal multicomponent 1,3-dipolar cycloaddition (1,3-DC) of diethyl aminomalonate or α-amino esters (derived from glycine, alanine, phenylalanine, and phenylglycine) with ethyl glyoxylate and the corresponding dipolarophile such as maleimides, methyl acrylate, methyl fumarate, (*E*)-1,2-bis(phenylsulfonyl)ethylene, and electron deficient alkynes allows the diastereoselective synthesis of new polysubstituted pyrrolidine derivatives. Microwave-assisted heating processes give better results than conventional heating ones, affording *endo*-cycloadducts as major stereoisomers. In general, 2,5-*cis*-cycloadducts are preferentially formed according to the previous formation of the W-shaped dipole. Only in the 1,3-DC of the disulfone with phenylglycine and ethyl glyoxylate the corresponding *exo*-*trans*-cycloadduct was isolated. The compound *endo*-*cis*-**4b**, derived from phenylalanine, ethyl glyoxylate and *N*-benzylmaleimide, has been further transformed into a very complex diazabicyclo[2.2.1]octane skeleton with potential biological activity.

Introduction

The use of multicomponent reactions (MCRs)[1] in organic synthesis allows the efficient preparation of a wide range of complex molecules in an economically favourable way by using simple processes. In the case of 1,3-dipolar cycloadditions (1,3-DC)[2] of azomethine ylides and dipolarophiles, generally, the corresponding imino esters have to be prepared previously from the carbonyl compound and the α-amino acid to yield highly substituted prolines.[3–5] This core heterocyclic structure is readily involved in diversity-oriented synthesis (DOS)[6] allowing the preparation of different small structures in a reduced number of synthetic steps.

However, few examples of 1,3-DC of azomethine ylides have been described using MCR.[7] In all of these examples, aromatic carbonyl compounds and amino esters have been combined affording the corresponding prolines bearing at the 5-position an aromatic or heteroaromatic ring. Alternatively, the use of ethyl glyoxylate as the aldehyde component would allow the synthesis of 2,5-bis(alkoxycarbonyl)-substituted pyrrolidines **I** by means of 1,3-DC (Scheme 1). In this particular situation, the preparation and isolation of imino esters is very difficult due to their instability. Therefore, in the only described contribution using ethyl glyoxylate and ethyl *N*-(1-phenylethyl)glycinate, the 1,3-DC had to be performed in a multicomponent process affording a mixture of pyrrolidines **II–V** with very low diastereoselection (Scheme 2).[8]



Scheme 1 Retrosynthetic analysis for the synthesis of **I**.

In this work, we describe for the first time the employment of the very reactive ethyl glyoxylate as the aldehyde component in a general domino-MCR, involving *in situ* generation of the imino esters, followed by a [1,2]-prototropy shift, and further thermal 1,3-DC with electrophilic alkenes or alkynes, for the general synthesis of prolines **I**.

Results and discussion

For initial studies, diethyl aminomalonate was chosen as an appropriate and more reactive candidate to undergo this type of multicomponent 1,3-DC.[7a–d] The model reaction between commercially available ethyl glyoxylate (50% solution in

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†Dedicated to the memory of Prof. Balbino Mancheño.

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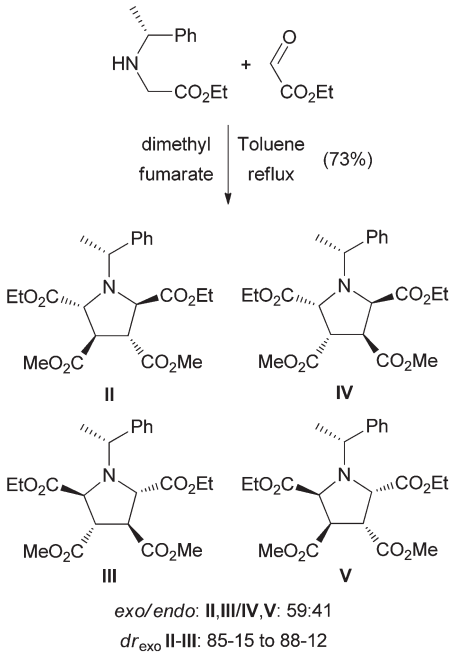
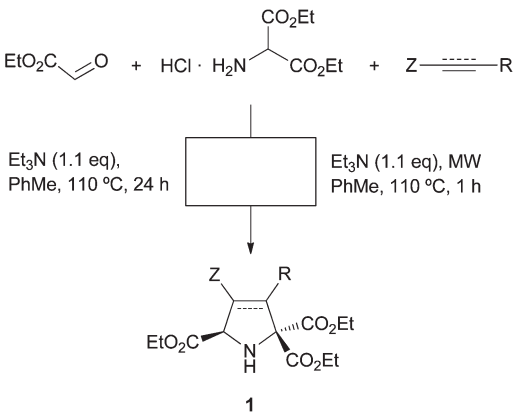


Scheme 2 Published example using ethyl glyoxylate in a multicomponent 1,3-DC.



Scheme 3 1,3-DC involving diethyl aminomalonate.

toluene) diethyl aminomalonate hydrochloride and *N*-methylmaleimide, in the presence of triethylamine (1.1 equiv.), was tested using several solvents under conventional heating (CH) or through microwave (MW)-assisted heating.[9] Good conversions and stereoselections of cycloadducts **1** were achieved by using toluene as the pure solvent by heating at 110 °C for 24 h (Scheme 3). Moreover, the multicomponent microwave-assisted transformation afforded a cleaner crude reaction mixture probably due to the faster reaction (1 h) of the *in situ* generated azomethine ylide with the dipolarophile.

The scope of this 1,3-DC was studied with several dipolarophiles (Scheme 3 and Fig. 1). In the case of maleimides such as *N*-methyl, *N*-benzyl, and *N*-phenyl maleimides (NMM, NBM, and NPM, respectively) pure *endo*-cycloadducts **1a–c** were isolated in very good yields and diastereoselectivity. Dimethyl

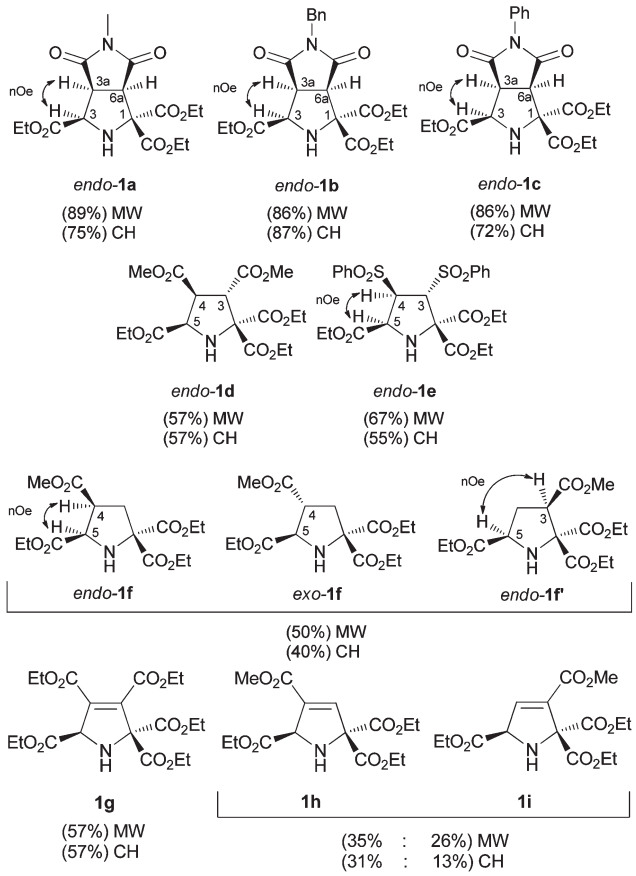


Fig. 1 1,3-DC of ethyl glyoxylate and diethyl aminomalonate in toluene.

fumarate furnished *endo*-**1d** in relatively good yield (57% regardless of the selected heating mode). (*E*)-1,2-Bis(phenylsulfonyl)ethylene, a synthetic equivalent of acetylene, was also assessed giving disulfone *endo*-**1e** in higher yield (67%) when the reaction took place under microwave irradiation. In the case of methyl acrylate an excess (10 equiv.) was required affording, under both heating conditions (MW and CH), a mixture of two *endo*-**1f**, and *exo*-**1f** stereoisomers and regioisomer *endo*-**1f′** (3 : 3 : 1) in moderate yields (Fig. 1).

Then acetylenic dipolarophiles were assayed. Symmetrical diethyl acetylenedicarboxylate afforded Δ^3-pyrroline **1g** (Fig. 1) in moderate yield (57%). An unexpected result was obtained in the thermal multicomponent reaction involving methyl propiolate. The reaction occurred in the presence of 3 equiv. of the dipolarophile in 61 and 44% overall yields under microwave-assisted and conventional heating, respectively. The corresponding products were isolated as a mixture of two regioisomers **1h** and **1i** in equal proportions (Fig. 1).

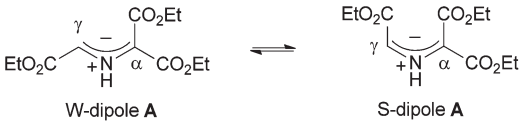
The relative configuration of products **1** was determined employing bidimensional NMR experiments (NOESY, COSY, HSMC, *etc.*) and by comparison of the experimental coupling constants with those reported in the literature for related structures.[10] For example, positive NOESY experiments and coupling constants of 8.5 Hz for the *cis*-arrangements H_3–H_{3a} and H_{3a}–H_{6a} supported the skeleton represented by *endo*-**1a**, **1b**

and **1c** structures. The higher chemical shift observed for H_{6a} (4.1–4.4 ppm, in *cis*-position with respect to an ester group) *versus* a range of 3.85–4.00 ppm for H_{6a} supported this arrangement. For the cases of *endo*-cycloadducts **1d** and **1e**, derived from 1,2-*trans*-disubstituted alkenes, both of the *cis*- and *trans*-coupling constants are very similar. NOESY experiments did not clarify the relationship of hydrogen atoms bonded at positions 3, 4 and 5 of the heterocycle of compound **1d**, but the chemical shifts of H_3 and H_5 matched with the structure represented in Fig. 1 according to the previous comment (see above). This assignment was also confirmed by the structural analysis of the molecule *endo*-**1e**, which displayed a very important positive nOe between *cis*-H_4–H_5. The observed coupling constant [$J(H_4–H_5)$ = 4.7 Hz] was slightly higher than the corresponding *trans*-H_3–H_4 (3.7 Hz), although with a lower absolute value than the analogous one observed for maleimide derivatives. Chemical shifts 4.64 ppm (H_4 in *trans*-position with respect to CO_2Et) and 5.15 ppm (H_3 in *cis*-position with respect to CO_2Et) were considered as definitive parameters to resolve the relative configuration.

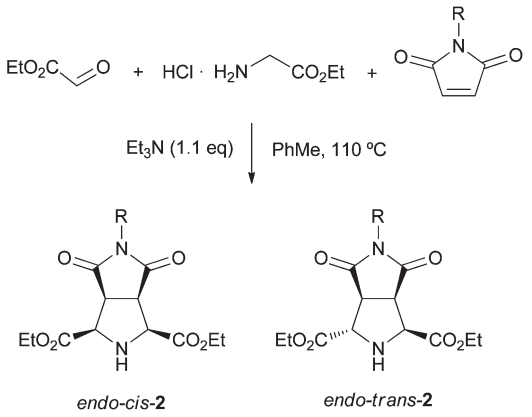
The mixture of compounds **1f** was more difficult to elucidate because crucial signals appeared in very narrow ranges of ppm and also the stereoisomers could not be separated by flash chromatography. Compound *endo*-**1f** was identified according to the $J(H_4–H_5)$ = 8.2 Hz by comparison with the analogous data obtained for the *cis*-arrangement observed for cycloadduct *endo*-**1d**, and by nOe experiments. In addition, the other stereoisomer possesses a signal, with $J(H_4–H_5)$ = 6.9 Hz, which is appropriate for a *trans*-arrangement of those hydrogen atoms. Regioisomer *endo*-**1f'**, also observed in other examples of cycloaddition performed with methyl acrylate (see below), was identified in less proportion as the all-*cis* substituent pyrrolidine (confirmed by a small H_3–H_5 nOe) as a consequence of the attack of the W-shaped dipole **A** through its γ-position (Scheme 4).

In this series, the microwave-assisted reaction was much more advantageous. Surprisingly, when a freshly distilled ethyl glyoxylate was employed in this MCR the crude reaction mixture was extremely complex to analyze (^{1}H NMR). It is worth noting the importance of this multicomponent process because attempts to prepare the imine derived from diethyl aminomalonate and ethyl glyoxylate failed.

Encouraged by the good diastereoselection and simplicity of these reactions, we decided to explore the analogous transformation using α-amino esters. First, glycine ethyl ester was used for the synthesis of cycloadducts **2** under the previously described reaction conditions (Scheme 5). Microwave-assisted heating (1 h) provided similar conversions, chemical yields



Scheme 4 Dipole conformations derived from ethyl glyoxylate and diethyl aminomalonate.



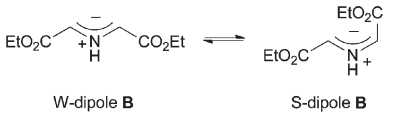
Scheme 5 1,3-DC of ethyl glycinate and ethyl glyoxylate with maleimides.

Table 1 1,3-DC between ethyl glycinate, ethyl glyoxylate, and maleimides

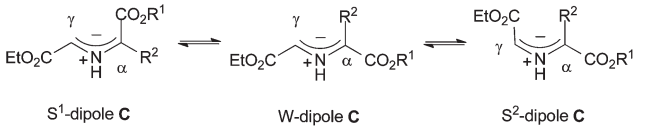
Entry	R	Heating[a]	Con.[b] (%)	2	Yield[c] (%)	*cis*/*trans*[b,d]
1	Me	CH	100	**2a**	75	3 : 1 (2 : 1)
2	Me	MW	100	**2a**	80	3 : 1 (2 : 1)
3	Bn	CH	100	**2b**	64	1 : 1 (2 : 1)
4	Bn	MW	85	**2b**	60	1 : 1 (2 : 1)
5	Ph	CH	100	**2c**	71[e]	>20 : 1 (4 : 1)
6	Ph	MW	96	**2c**	70[e]	>20 : 1 (4 : 1)

[a] Conventional heating (CH) takes 24 h for completion whilst microwave-assisted heating (MW) needs 1 h. [b] Determined by ^{1}H and ^{13}C NMR analysis. [c] Isolated yield after flash chromatography. [d] In brackets the diastereomeric ratio determined in the crude product. [e] Yield for compound *endo-cis*-**2c**.

and faster reactions than the analogous processes performed under conventional heating (24 h) (Table 1). Again, MW heating afforded cleanest crude reaction mixtures by ^{1}H NMR, without signals of the corresponding polymer from ethyl glyoxylate. Symmetrical dipolarophiles such as *N*-methyl, *N*-benzyl, and *N*-phenyl maleimides (NMM, NBM, and NPM, respectively) were evaluated affording cycloadducts **2** in moderate to good yields (Table 1). Nevertheless, the *cis*/*trans* ratio (referred to both CO_2Et group arrangement) of the final bicycle **2** was unexpectedly very different. Thus, NMM and NPM furnished *endo-cis*-**2a** as the major stereoisomer (Table 1, entries 1, 2, 5 and 6). However, NBM afforded equimolar amounts of both *cis*- and *trans*-isomers **2b**. The relative stereochemistry of the major *endo-cis*-**2c** was determined through NOESY experiments and by comparison of its X-ray diffraction pattern[11] with the analogous one described for a similar compound to **2c** (prepared in a fullerene-sensitized 1,3-DC between maleimides and iminodiacetic acid).[12] As was described in this last contribution the second order coupling constant did not confirm the higher value for the *cis*-arrangement. However, for the *endo-trans*-isomers a *cis*-coupling constant was observed (8.0–8.1 Hz) and smaller coupling constants in the corresponding multiplet. The imine derived from ethyl glycinate and ethyl glyoxylate could not be isolated in spite of testing several conditions and dehydrating protocols. We assume that in the case



Scheme 6 Dipole conformations derived from glycine ethyl ester and ethyl glyoxylate.



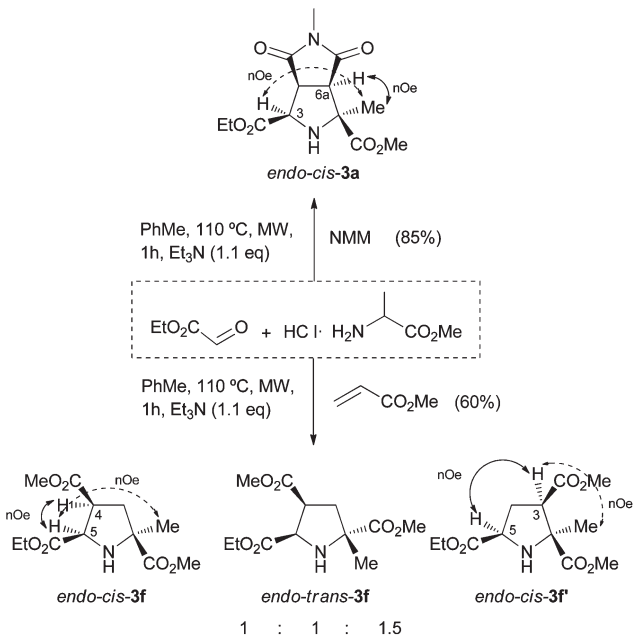
Scheme 8 Dipole conformations derived from α-substituted amino esters and ethyl glyoxylate.

of NMM and NPM the W-shaped ylide **B** reacts preferentially than the S-shaped one **B** affording mainly the 2,5-*cis* substituted pyrrolidine (Scheme 6).

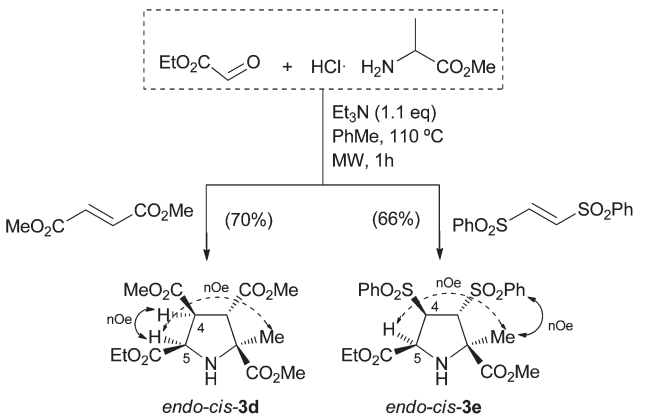
The described reaction involving maleimides and glycine ethyl ester hydrochloride afforded symmetrical arrangement in structures **2**. In order to study the effect of a non-symmetrical alkene, the MW-assisted reaction was performed, in toluene as the solvent, with several dipolarophiles such as methyl acrylate, dimethyl fumarate, (*E*)-1,2-bis(phenylsulfonyl)ethylene or methyl propiolate. In all these examples, mixtures of unidentified isomers were obtained in low yields presumably due to epimerizations mainly at the 2- and/or 5-position of the pyrrolidine ring.

The microwave-assisted heating was next applied to the synthesis of more substituted pyrrolidine derivatives **3**, where methyl alaninate was selected as the dipole precursor combined with NMM and methyl acrylate as dipolarophiles (Scheme 7). In the reaction involving NMM the product *endo-cis*-**3a** was stereoselectively obtained in very good chemical yield (85%). The coupling constants of the cyclic hydrogen atoms were 8.0 Hz (*cis*-arrangement). Also, a small nOe between the methyl group and the H_3, H_{3a} or H_{6a} hydrogen atoms was observed. The reaction carried out in the presence of methyl acrylate was not so diastereoselective obtaining a mixture of *endo-cis*-regioisomers **3f** and **3f′** together with the stereomutated adduct *endo-trans*-**3f** (Scheme 7) originated by means of the S^1-dipole **C** (R^2 = Me, Scheme 8). The presence of an important amount of *endo-cis*-**3f′** implies that the isomerization of the imino ester occurred towards the formation of the thermodynamically more substituted resonance form of W-dipole **C** (R^2 = Me, Scheme 8) allowing the attack of the dipole by its γ-position. The analogous reaction with *tert*-butyl acrylate gave a very poor yield of an unidentified mixture of products. In any case involving acrylates, the reaction carried out under conventional heating afforded lower chemical yields (34–37%). The relative configuration of compound *endo-cis*-**3f** was determined according to H_4–H_5 nOe and very small nOe between the methyl group and H_5. The presence of this substituent in the ring reduced the *cis*-coupling constant to a 7.0 Hz value, which was also observed for the *endo-trans*-**3f**. For the last compound **3f′**, NOESY experiments were very helpful because intense nOe was shown between H_3–H_5 and also by the methyl group with H_3.

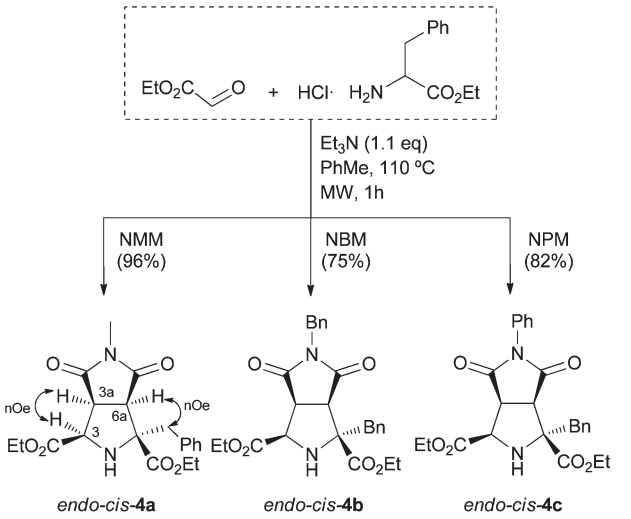
Lower LUMO-alkenes such as dimethyl fumarate and (*E*)-1,2-bis(phenylsulfonyl)ethylene were next examined as dipolarophiles in this multicomponent transformation (Scheme 9). In both examples, the reaction was highly diastereoselective obtaining the corresponding *endo-cis*-cycloadducts **3d** and **3e** in good yields after flash chromatography (70 and 66% yield, respectively). Apparently, other different stereoisomers were not detected either from the ^{1}H NMR reaction crude or by analysis of the purified compounds. The nature of substituents in a small-size carbocycle can alter their *cis*- and *trans*-coupling constants, thus, the reaction employing fumarate, with



Scheme 7 1,3-DC involving ethyl alaninate, ethyl glyoxylate with NMM or methyl acrylate.



Scheme 9 1,3-DC of methyl alaninate and ethyl glyoxylate with dimethyl fumarate or (*E*)-1,2-bis(phenylsulfonyl)ethylene.

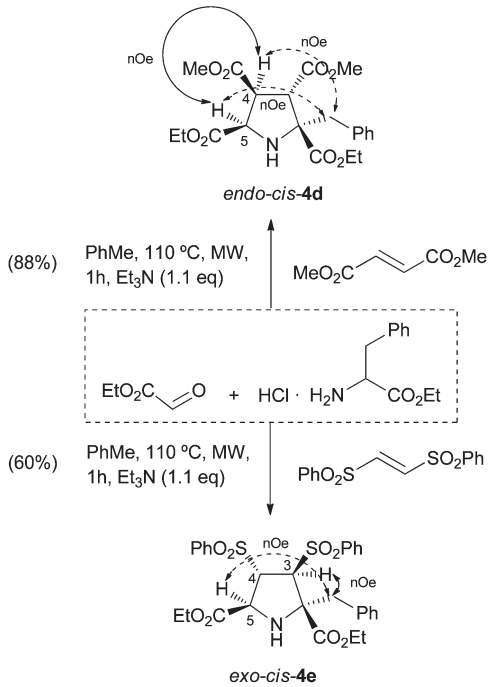


Scheme 10 1,3-DC of ethyl phenylalaninate and ethyl glyoxylate with maleimides.

$J_{cis}H_4$–H_5= 8.0 Hz, is clearly lower than the $J_{trans}H_3$–H_4= 10.0 Hz for the compound *endo-cis*-**3d** (also observed in compounds *endo-cis*-**4d** and *endo-cis*-**5d**, see below). Nevertheless, phenylsulfonyl substituents maintained the higher coupling constant for the *cis*-arrangement $J(H_4$–$H_5)$ = 6.5 Hz *versus* a 4.5 Hz value given by a *trans*-H_3–H_4 junction, such as occurred in every cycloadduct of this work derived from this disulfone. A very small nOe was detected between the methyl group and H_5 and a small one with the sulfonyl aromatic ring too (Scheme 9).

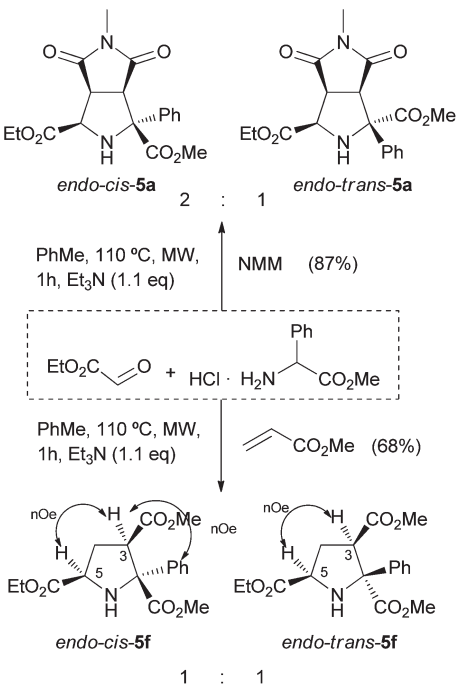
Similar behaviour was observed when the microwave-assisted heating was employed in the cycloaddition of ethyl phenylalaninate, ethyl glyoxylate and dipolarophiles. Maleimides were suitable electrophilic alkenes, for example NMM, NBM and NPM afforded exclusively, under the standard reaction conditions, products *endo-cis*-**4** in 96, 75, and 82% yield, respectively (Scheme 10). The corresponding $J_{cis}H_3$–H_{3a} coupling constants were 8.4 Hz for *endo-cis*-**4a**, and 7.8 Hz for both *endo-cis*-**4b** and **c**. The benzylic substituent is in a *cis*-position with respect to H_3–H_{3a}–H_{6a} according to NOESY experiments.

Dimethyl fumarate and phenylalaninate ethyl ester hydrochloride afforded cycloadduct *endo-cis*-**4d** in higher yield than the corresponding one obtained in the reaction using the alaninate (Scheme 11). The $J_{trans}H_3$–H_4 (10.1 Hz) and the $J_{cis}H_4$–H_5 (8.5 Hz) were similar to those observed for compound *endo-cis*-**3d**. A nOe was observed between benzylic protons and both H_4 and H_5. When disulfone (*E*)-1,2-bis(phenylsulfonyl)ethylene was allowed to react with ethyl phenylalaninate and ethyl glyoxylate, cycloadduct *exo-cis*-**4e** was obtained in 60% yield as the major diastereoisomer (*exo*/*endo* > 20 : 1, Scheme 11). Its relative configuration was determined by strong positive benzylic hydrogen atoms – H_3 nOe and a noticeable nOe between this benzylic methylene and H_5. In addition, a double J_{trans} = 5.2 Hz was observed in the H_4 signal. This opposite diastereoselectivity observed (in comparison with the diethyl aminomalonate adduct **1e** or *endo-cis*-**3e**) could be caused by steric repulsions of the benzylic substituent with the sulfonyl group.



Scheme 11 1,3-DC of ethyl phenylalaninate and ethyl glyoxylate with dimethyl fumarate or (*E*)-1,2-bis(phenylsulfonyl)ethylene.

Another interesting series of α-quaternized pyrrolidine derivatives were isolated from the microwave assisted cycloaddition between methyl phenylglycinate hydrochloride, ethyl glyoxylate and different dipolarophiles (Scheme 12). Firstly, NMM afforded a 2 : 1 mixture of *endo*-cycloadducts, the



Scheme 12 1,3-DC of methyl phenylglycinate and ethyl glyoxylate with NMM or methyl acrylate.

stereomutated product being the minor isomer. The double *cis*-coupling constants for H_3–H_{3a} and H_{3a}–H_{6a} (8.5 and 7.5 Hz, respectively), and the positive nOe of H_3–H_{3a}–H_{6a} to each other supported the structure drawn for *endo-cis*-**5a** in Scheme 12. In the case of the *endo-trans*-**5a** the same positive nOe of H_3–H_{3a}–H_{6a} was detected (*cis*-coupling constants around 7.6 Hz) but the H_3 chemical shift (4.25 ppm) appeared at lower fields than the corresponding H_3 chemical shift (3.96 ppm) of the product *endo-cis*-**5a**. In the reaction performed with methyl acrylate the resulting regioselection was very high, however, the diastereoselection was similar to that described previously for NMM. The equimolar ratio of *endo-cis*-**5f**/*endo-trans*-**5f** was identified by ^{1}H NMR and the assignment of both relative configurations by NOESY experiments, specially by the nOe exhibited by H_3 with aromatic protons in cycloadduct *endo-cis*-**5f**. In both *endo-cis*-**5f** and *endo-trans*-**5f** a weak H_3–H_5 nOe was identified (Scheme 12). According to these results the S^1-dipole **C** (Scheme 8, R^1 = Me, R^2 = Ph) could be the precursor of *endo-trans*-cycloadducts. Due to steric reasons this dipole S^1-**C** reacted preferentially through its γ-position.

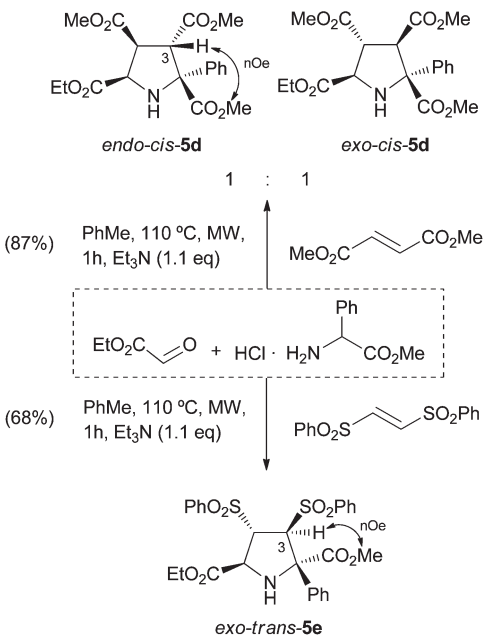
Dimethyl fumarate furnished an equimolecular mixture of diastereoisomers *endo-cis*-**5d** and *exo-cis*-**5d** in 87% yield (Scheme 13). For the *endo-cis*-arrangement J_{trans} was 10.1 Hz and 8.5 Hz for J_{cis}, and also H_3-CO_2Me nOe data were valuable to assign the final structure. The e*xo-cis*-**5d** compound showed all-*trans* coupling constants 6.7 and 6.9 Hz, and a clear H_3-Ph nOe. From the analysis of chemical shifts of the H_3 atom in compounds **5a**, **5d** and **5f**, when this atom is in almost eclipsed conformation (*cis*-relative position) with the methyl ester group (bonded to C_2) it is deshielded by around 0.3, 0.4, and 0.5 ppm, respectively, with respect to the analogous shift appearing when H_3 and the phenyl group are in a *cis*-junction.

With all this information, it was possible to elucidate the structure of cycloadduct *exo-trans*-**5e**, which was obtained, in 68% yield, under standard reaction conditions employing (*E*)-1,2-bis(phenylsulfonyl)ethylene, ethyl glyoxylate and phenylglycine methyl ester hydrochloride (Scheme 13). Again, all-*trans* coupling constants 5.3 and 5.0 Hz, and H_3-CO_2Me nOe supported the drawn structure. However, the most relevant detail was the H_3 chemical shift (4.86 ppm), which is around 0.35 ppm higher than, for example, the chemical shift of H_3 in disulfonylated cycloadducts *exo-cis*-**4e** or *endo-cis*-**3e**.

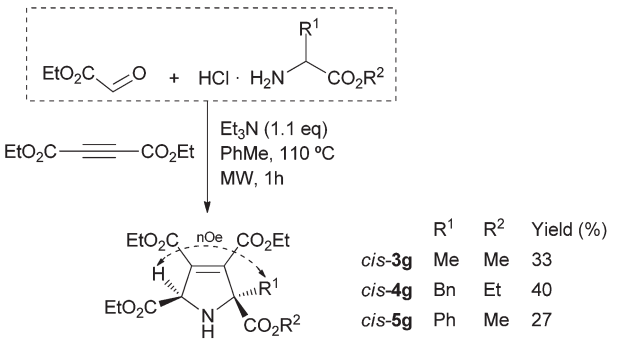
According to very simple MM3 force field free energy calculations[13] the formation of the most energetically favoured stereoisomer *exo-trans*-**5e** was confirmed. Despite the apparent low difference in energy between the two resonance forms of S^1-dipole **C** (Scheme 8, R^1 = Me, R^2 = Ph) it seems that the bulky disulfone is better approached in an *exo*-manner due to possible hydrophobic interactions between a phenylsulfonyl ring and the phenyl group of the dipole.

Cycloadditions involving electron poor alkynes deserve a special mention. Methyl propiolate and diethyl acetylenedicarboxylate were appropriate dipolarophiles in the reaction performed with diethyl aminomalonate (Fig. 1). However, when glycinate, alaninate, phenylalaninate, and phenylglycinate were used for the 1,3-DC with methyl propiolate, the reaction mixture was extremely complex and no cycloadduct could be isolated. However, when α-substituted amino esters were allowed to react with ethyl glyoxylate and diethyl acetylenedicarboxylate, cycloadducts *cis*-**3g**, *cis*-**4g** and *cis*-**5g** were isolated after purification (flash chromatography) in moderate yields and as pure *cis*-stereoisomers (Scheme 14). In these three examples nOes between H_5 and the corresponding substituent (R^1) were observed.

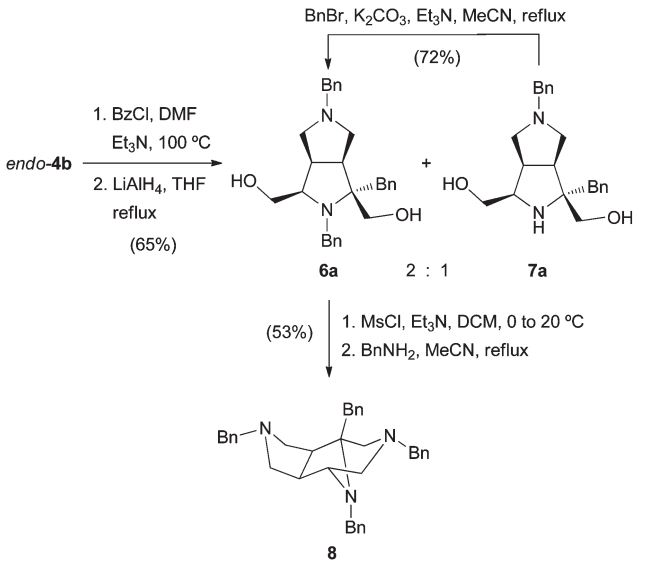
This type of 1,3-DC permits the generation of pyrrolidine rings incorporating two alkoxycarbonyl groups, in many cases, with a *cis*-2,5-arrangement which is very valuable from the synthetic point of view because it is not a very easy task. As a possible application, we were interested in the synthesis of the bicyclic system **8**, which can be employed for the elaboration of large series of biologically active compounds.[14] For this



Scheme 13 1,3-DC of methyl phenylglycinate and ethyl glyoxylate with dimethyl fumarate or (*E*)-1,2-bis(phenylsulfonyl)ethylene.



Scheme 14 1,3-DC of amino esters and ethyl glyoxylate with diethyl acetylenedicarboxylate.



Scheme 15 Synthesis of the biologically active compound **8**.

purpose, cycloadduct *endo*-**4b** was allowed to react with benzoyl chloride[15] and the resulting amide immediately reduced in the presence of lithium aluminum hydride obtaining a 2 : 1 mixture of the desired diol **6a** and the debenzylated bicycle **7a** in 65% combined yield (Scheme 15). The latter was successfully transformed to **6a** in 78% yield by alkylation with benzyl bromide in DMF at 100 °C. The final diazabicyclo[2.2.1]-octane skeleton of **8** was achieved by a known methodology[16] employing a double mesylation followed by a ring closing nucleophilic substitution performed by benzylamine after 19 h under refluxing acetonitrile. The *all-cis*-**8** compound was isolated as a unique diastereoisomer in 53% yield, and a 34% overall yield from cycloadduct *endo*-**4b** (Scheme 15).

In conclusion, commercially available toluene solutions of reactive ethyl glyoxylate could be incorporated into the multicomponent 1,3-DC of azomethine ylides with dipolarophiles. Microwave-assisted heating was much more effective than the conventional heating affording total conversions in 1 h and cleaner reaction products in all the examples described across the text. If we analyze the effect of the 1,3-dipole nature, the normal trend of aminomalonate derived heterocycles is to react as its W-shaped type **A**, **B** or **C** 1,3-dipole (Schemes 4, 6 and 8) finding an exception when methyl acrylate was used as the dipolarophile. W-Shaped 1,3-dipole **B** (Scheme 6) is the most abundant intermediate when glycine ethyl ester was involved in the cycloaddition, although the existence of the S-shaped-**B** (Scheme 6) 1,3-dipole is noticeable. α-Substituted amino esters such as alanine methyl ester or phenylalanine ethyl ester overwhelmingly reacted through their W-shaped type **C** 1,3-dipoles. However, in the reactions dealing with the more sterically hindered phenylglycine derivative a competition of the attack through both α- and γ-positions of S^1-dipole **C** (Scheme 8) was inferred. In fact, S^1-dipole **C** precursor exclusively reacted by its γ-position when the ethylenic disulfone was employed.

According to the dipolarophiles, maleimides afforded exclusively *endo*-cycloadducts as well as dimethyl fumarate and methyl acrylate. Nevertheless, (*E*)-1,2-bis(phenylsulfonyl)ethylene reacted in a different manner depending on the amino ester. Thus, the *endo*-approach prevailed for less hindered R^2 substituents (amino malonate and alanine derivatives), meanwhile the *exo*-type interaction was favoured by phenylalanine and phenylglycine surrogates.

Finally, diethyl acetylenedicarboxylate afforded just one stereoisomer always operating under a W-shaped type **A** or **C** 1,3-dipole geometry. Methyl propiolate could only be tested in the reaction with diethyl aminomalonate affording an equimolar mixture of regioisomers as a consequence of the competition of the attack of the W-shaped type **A** dipole through its γ-position (Scheme 4).

Further studies to improve both regio- and diastereoselection by lowering the temperature of the reaction by means of an efficient catalyst are currently underway.

Experimental

General

The structurally most important peaks of the IR spectra (recorded using a Nicolet 510 P-FT and a Jasco FTIR 4100) are listed. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained using a Bruker AC-300 with $CDCl_3$ as the solvent and TMS as the internal standard unless otherwise stated. Low-resolution electron impact (GC-EI) mass spectra were obtained at 70 eV using a Shimadzu QP-5000, and high-resolution mass spectra were obtained using a Finnigan VG Platform. HRMS (GC-EI) were recorded using a Finnigan MAT 95S instrument. Analytical TLC was performed using Schleicher & Schuell F1400/LS silica gel plates, and the spots were visualized under UV light (λ = 254 nm). Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. For flash chromatography, we employed Merck silica gel 60 (0.040–0.063 mm). CEM Discover and Explorer-Coolmate accessories were employed in the microwave-assisted reactions for the generation of imino esters.

General procedure for the microwave-assisted synthesis of cycloadducts

Ethyl glyoxylate (100 μL, 0.5 mmol, 50% in toluene), diethyl aminomalonate hydrochloride or the amino acid ethyl ester hydrochloride (0.5 mmol), the corresponding dipolarophile (0.5 mmol) and triethylamine (90 μL, 0.55 mmol) were dissolved in toluene (4 mL). The reaction vessel was sealed and irradiated in a CEM-discover microwave reactor at 110 °C and a maximum power of 60 W for 1 h. Alternatively, the reaction can be refluxed for 19 h. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate, washed with brine and dried over $MgSO_4$. After evaporation the residue was purified by flash chromatography (silica gel) to afford the corresponding product.

(3*R,3a*S**,6a*R**)-Triethyl 5-methyl-4,6-dioxo hexahydropyrrolo[3,4-*c*]pyrrole-1,1,3(2*H*)-tricarboxylate *endo*-1a.** Sticky pale yellow oil; R_f 0.24 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2983, 1701, 1731 cm^{-1}; ^1H NMR δ_H: 1.28–1.37 (m, 9H, 3 × $CO_2CH_2CH_3$), 2.93 (s, 3H, NCH_3), 3.42 (d, *J* = 10.5 Hz, 1H, N*H*), 3.60 [deform. dd, *J* = 8.5, 8.5 Hz, 1H, C*H*CH(CO_2Et)NH], 3.85 [dd, *J* = 10.5, 8.5 Hz, 1H, C*H*C(CO_2Et)NH], 4.15–4.45 [m, 7H, 3 × $CO_2CH_2CH_3$ and C*H*(CO_2Et)$_2$NH]; ^{13}C NMR δ_C: 13.8 ($CHCO_2CH_2CH_3$), 13.9 (2 × $CO_2CH_2CH_3$), 25.3 (NCH_3), 49.1 [*C*HCH(CO_2Et)NH], 51.6 [*C*HC(CO_2Et)$_2$NH], 61.2 [*C*H(CO_2Et)NH], 61.3, 61.9 (2 × $CO_2CH_2CH_3$), 62.9($CO_2CH_2CH_3$), 75.3 [*C*(CO_2Et)$_2$], 166.1, 168.5, 168.6 (3 × $CO_2CH_2CH_3$), 174.4, 174.6 (2 × CON); MS (EI-GC) *m*/*z*: 370 (M^+ + 1, <1%), 298 (15), 297 (100), 166 (56), 138 (11), 94 (15), 93 (10); HRMS calculated for $C_{16}H_{22}N_2O_8$: 370.1336, found: 370.1337.

(3*R,3a*S**,6a*R**)-Triethyl 5-benzyl-4,6-dioxohexahydropyrrolo-[3,4-*c*]pyrrole-1,1,3(2*H*)-tricarboxylate *endo*-1b.** Sticky pale yellow oil; R_f 0.39 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2939, 2984, 2341, 2360, 1734, 1708 cm^{-1}; ^1H NMR δ_H: 1.24–1.34 (m, 9H, 3 × $CO_2CH_2CH_3$), 3.62 [deform. dd, *J* = 8.5 and 8.5 Hz, 1H, C*H*CH(CO_2Et)NH], 3.88 [d, *J* = 8.5 Hz, 1H, C*H*C(CO_2Et) NH], 4.14–4.43 [m, 7H, 3 × $CO_2CH_2CH_3$ and C*H*(CO_2Et)$_2$NH], 4.59 (s, 2H, CH_2Ph), 7.32–7.26 (m, 5H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 14.0 ($CHCO_2CH_2CH_3$), 14.1 (2 × $CO_2CH_2CH_3$), 43.1 (CH_2Ph), 49.3 [*C*HCH(CO_2Et)NH], 51.8 [*C*HC(CO_2Et)$_2$NH], 61.7 [*C*H(CO_2Et)NH], 62.2, 63.0, 63.1 (3 × $CO_2CH_2CH_3$), 75.7 [*C*(CO_2Et)$_2$], 128.1, 128.6, 128.7, 135.2 (Ar*C*), 166.2, 168.6, 168.7 (3 × $CO_2CH_2CH_3$), 174.2, 174.4 (2 × CON); MS (EI-GC) *m*/*z*: 446 (M^+ + 1, <1%), 374 (21), 373 (100), 227 (11), 166 (33), 94 (11), 91 (42); HRMS calculated for $C_{22}H_{26}N_2O_8$: 446.1689, found: 446.1688.

(3*R,3a*S**,6a*R**)-Triethyl 4,6-dioxo-5-phenylhexahydropyrrolo-[3,4-*c*]pyrrole-1,1,3(2*H*)-tricarboxylate *endo*-1c.** Sticky pale yellow oil; R_f 0.29 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2983, 2939, 2906, 1714 cm^{-1}; ^1H NMR δ_H: 1.25–1.37 (m, 9H, 3 × $CO_2CH_2CH_3$), 3.64 (d, *J* = 10.0 Hz, 1H, N*H*), 3.78 [dd, *J* = 8.4, 7.9 Hz, 1H, C*H*CH(CO_2Et)NH], 4.00 [dd, *J* = 10.0, 8.4 Hz, 1H, C*H*C(CO_2Et)NH], 4.16–4.45 [m, 7H, 3 × $CO_2CH_2CH_3$ and C*H*-(CO_2Et)$_2$NH], 7.15–7.23 (m, 2H, Ar*H*), 7.47–7.33 (m, 3H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 14.0 ($CHCO_2CH_2CH_3$), 14.1 (2 × $CO_2CH_2CH_3$), 49.6 [*C*HCH(CO_2Et)NH], 52.1 [*C*HC(CO_2Et)$_2$NH], 62.1 [*C*H(CO_2Et)NH], 62.3, 63.1, 63.2 (3 × $CO_2CH_2CH_3$), 76.2 [*C*(CO_2Et)$_2$], 126.7, 129.1, 129.4, 131.5 (Ar*C*), 166.4, 168.7, 169.0 (3 × $CO_2CH_2CH_3$), 173.8, 174.0 (2 × CON); MS (EI-GC) *m*/*z*: 432 (M^+ + 1, <1%), 360 (20), 359 (100), 166 (58), 138 (12), 94 (19); HRMS calculated for $C_{21}H_{24}N_2O_8$: 432.1533, found: 432.1544.

(3*S,4*S**,5*R**)-2,2,5-Triethyl 3,4-dimethyl pyrrolidine-2,2,3,4,5-pentacarboxylate *endo*-1d.** Yellow pale oil; R_f 0.34 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2984, 2956, 2910, 1732 cm^{-1}; ^1H NMR δ_H: 1.20–1.30 (m, 9H, 3 × $CO_2CH_2CH_3$), 3.56 [deform. dd, *J* = 9.0, 8.0 Hz, 1H, C*H*CH(CO_2Et)NH], 3.68–3.75 [m with 2 × s, 7H, 2 × CO_2CH_3, C*H*C(CO_2Et)NH], 4.08 [d, *J* = 9.0 Hz, 1H, C*H*(CO_2Et)$_2$], 4.10–4.32 (m, 6H, 3 × $CO_2CH_2CH_3$), N*H* nd; ^{13}C NMR δ_C: 13.9 ($CHCO_2CH_2CH_3$), 14.0, 14.2 (2 × $CO_2CH_2CH_3$), 50.5 [*C*HCH(CO_2Et)NH], 52.6 [*C*HC-(CO_2Et)$_2$NH], 52.7, 53.4 (2 × CO_2CH_3), 61.8 [*C*H(CO_2Et)NH], 61.9, 62.7, 62.7 (3 × $CO_2CH_2CH_3$), 74.6 [*C*(CO_2Et)$_2$], 168.7, 168.9, 170.3, 171.0, 171.2 (5 × CO_2CH_3); MS (EI-GC) *m*/*z*: 403 (M^+ + 1, <1%), 299 (15), 298 (100), 198 (23), 166 (47), 152 (15), 138 (10), 119 (10), 94 (11); HRMS calculated for $C_{17}H_{25}NO_{10}$: 403.1478, found: 403.1490.

(3*R,4*R**,5*S**)-Triethyl 3,4-bis(phenylsulfonyl)pyrrolidine-2,2,5-tricarboxylate *endo*-1e.** Pale yellow prisms, mp = 49–51 °C (from hexane–ethyl acetate); R_f 0.11 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 3105, 2360, 2341, 1747, 1265, 1153 cm^{-1}; ^1H NMR δ_H: 1.10 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.27 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.34 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 4.04 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.16 [d, *J* = 4.7 Hz, 1H, C*H* (CO_2Et)NH], 4.29–4.40 (m, 4H, 2 × $CO_2CH_2CH_3$), 4.64 [dd, *J* = 4.7, 3.7 Hz, 1H, C*H*CH(CO_2Et)NH], 5.15 [d, *J* = 3.7 Hz, 1H, C*H*(CO_2Et)$_2$NH], 7.45–7.74 (m, 8H, Ar*H*), 7.84–7.96 (m, 2H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 13.6 ($CHCO_2CH_2CH_3$), 13.8, 13.9 (2 × $CO_2CH_2CH_3$), 60.4 [*C*HCH-(CO_2Et)NH], 62.2, 63.3, 63.4 (3 × $CO_2CH_2CH_3$), 63.5 [*C*HC-(CO_2Et)$_2$NH], 68.3 [*C*H(CO_2Et)NH], 76.1 [*C*(CO_2Et)$_2$], 128.7, 129.0, 129.2, 129.3, 134.2, 134.3, 137.5, 138.2 (Ar*C*), 165.4, 167.5, 168.7 (3 × $CO_2CH_2CH_3$); MS (EI-GC) *m*/*z*: 567 (M^+ + 1, <1%), 495 (10), 494 (35), 353 (14), 352 (73), 306 (41), 280 (50), 235 (13), 234 (100), 212 (19), 166 (17), 141 (16), 140 (20), 125 (18), 120 (11), 112 (22), 94 (32), 77 (42), 68 (16); HRMS calculated for $C_{25}H_{29}NO_{10}S_2$–$C_3H_5O_2$: 494.0943, found: 494.0929.

(4*S,5*R**)-2,2,5-Triethyl 4-methylpyrrolidine-2,2,4,5-tetracarboxylate *endo*-1f and compound *exo*-1f.** Pale yellow oil; R_f 0.41 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2985, 1735 cm^{-1}; ^1H NMR δ_H: 1.20–1.29 (m, 2 × 9H, 3 × $CO_2CH_2CH_3$ *endo* + *exo*), 2.31–2.83 [m, 2 × 2H, $CH_2C(CO_2Et)_2$ *endo* + *exo*], 3.10 (br. s, 1H, NH), 3.64, 3.65 (2 × s, 2 × 3H, CO_2CH_3 *endo* + *exo*), 3.76 [deform. dd, *J* = 7.4, 7.2 Hz, 1H, C*H*CH(CO_2Et)NH *exo*], 3.88 [dd, 1H, *J* = 8.2, 6.9 Hz, C*H*CH(CO_2Et)NH *endo*], 4.09 [d, *J* = 8.2 Hz, 1H, C*H*(CO_2Et)NH *endo*], 4.12–4.30 [m, 13H, 6 × $CO_2CH_2CH_3$ *endo* + *exo* C*H*(CO_2Et)NH *exo*]; ^{13}C NMR δ_C: 14.0, 14.1, 14.1, 14.2, 14.2, 14.3 (6 × $CO_2CH_2CH_3$ *endo* + *exo*), 33.5, 34.6 [2 × $CH_2C(CO_2Et)_2$NH *endo* + *exo*], 46.8, 49.5 [2 × *C*H-(CO_2Et)NH *endo* + *exo*], 52.2, 52.3 [2 × *C*HCH(CO_2Et)NH *endo* + *exo*], 59.1, 62.7 (2 × CO_2CH_3 *endo* + *exo*), 61.5, 61.6, 62.3, 62.5, 62.5, 62.6 (6 × $CO_2CH_2CH_3$ *endo* + *exo*), 71.6, 75.31 [2 × *C*(CO_2Et)$_2$ *endo* + *exo*], 168.9, 169.7, 170.3, 171.0, 171.3, 171.5, 171.9, 172.4 (8 × CO_2 *endo* + *exo*); MS (EI-GC) *m*/*z*: 345 (M^+ + 1, <1%), 273 (14), 272 (100), 140 (10), 170 (12), 94 (10), 68 (14); HRMS calculated for $C_{15}H_{23}NO_8$: 345.1434, found: 345.1441.

(*R*/*S*)-2,2,3,4,5-Pentaethyl 1*H*-pyrrole-2,2,3,4,5(5*H*)-pentacarboxylate 1g. Yellow oil; R_f 0.10 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2981, 2360, 2341, 1741 cm^{-1}; ^1H NMR δ_H 1.33–1.24 (m, 15H, 5 × $CO_2CH_2CH_3$), 4.14–4.32 (m, 10H, 5 × $CO_2CH_2CH_3$), 5.51 [s, 1H, C*H*(CO_2Et)NH], N*H* nd; ^{13}C NMR δ_C: 13.9, 14.0, 14.1, 14.1, 14.3 (5 × $CO_2CH_2CH_3$), 59.8, 62.1, 62.2, 62.5, 62.5 (5 × $CO_2CH_2CH_3$), 77.24 [*C*(CO_2Et)$_2$], 92.91 [*C*HC-(CO_2Et)$_2$NH], 146.9 [*C*CH(CO_2Et)NH], 147.0 [*C*C(CO_2Et)$_2$NH], 163.4, 166.7, 166.7, 166.8, 169.3 (5 × CO_2); MS (EI-GC) *m*/*z*: 429 (M^+ + 1, <1%), 345 (18), 300 (15), 299 (16), 273 (12), 272 (84), 227 (29), 226 (100), 199 (10), 198 (79), 181 (20), 170 (33), 154 (11), 142 (14), 125 (10), 124 (19), 87 (16), 69 (13), 68 (12);

microanalysis calculated for $C_{19}H_{27}NO_{10}$: C, 53.1; H, 6.3; N, 3.4%; found: C, 53.0; H, 6.0; N, 3.4%.

(*R*/*S*)-2,2,5-Triethyl 4-methyl 1*H*-pyrrole-2,2,4,5(5*H*)-tetracarboxylate 1h. Yellow oil; R_f 0.49 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2981, 2914, 1734, 1608 cm^{-1}; ^1H NMR δ_H: 1.19–1.33 (m, 9H, 3 × $CO_2CH_2CH_3$), 3.63 (s, 3H, CO_2CH_3), 4.09–4.31 (m, 6H, 3 × $CO_2CH_2CH_3$), 4.83 [d, *J* = 1.7 Hz, 1H, C*H*(CO$_2$Et)NH], 6.86 [d, *J* = 1.7 Hz, 1H, C*H*C(CO$_2$Et)$_2$], N*H* nd; ^{13}C NMR δ_C: 13.9 (3 × $CO_2CH_2CH_3$), 61.5 ($CO_2CH_2CH_3$), 62.6 (2 × $CO_2CH_2CH_3$), 62.8 (CO_2CH_3), 67.0 [*C*H(CO$_2$Et)NH], 79.0 [*C*(CO$_2$Et)$_2$NH], 150.8 [*C*HC(CO$_2$Et)$_2$NH], 150.9 [*C*CH(CO$_2$Et)NH], 162.60, 168.1, 168.2, 170.5 (4 × CO_2CH_3); MS (EI-GC) *m*/*z*: 343 (M^+ + 1, <1%), 270 (25), 226 (10), 198 (100), 170 (30), 166 (30), 152 (60), 126 (19), 122 (13), 120 (54), 94 (14); HRMS calculated for $C_{15}H_{21}NO_8$–$C_3H_5O_2$: 270.0980, found: 270.0995.

(*R*/*S*)-2,2,5-Triethyl 3-methyl 1*H*-pyrrole-2,2,3,5(5*H*)-tetracarboxylate 1i. Yellow oil; R_f 0.40 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2953, 1730, 1608 cm^{-1}; ^1H NMR δ_H: 1.19–1.33 (m, 9H, 3 × $CO_2CH_2CH_3$), 3.74 (s, 3H, CO_2CH_3), 4.09–4.31 (m, 6H, 3 × $CO_2CH_2CH_3$), 4.54 [d, *J* = 13.0 Hz, 1H, C*H*(CO$_2$Et)NH], 7.42 [d, *J* = 13.0 Hz, 1H, C*H*CH(CO$_2$Et)NH], N*H* nd; ^{13}C NMR δ_C: 13.9 (2 × $CO_2CH_2CH_3$), 14.0 ($CHCO_2CH_2CH_3$), 62.4 ($CHCO_2CH_2CH_3$), 62.5 (2 × $CO_2CH_2CH_3$), 62.8 (CO_2CH_3), 66.2 [*C*H(CO$_2$Et)NH], 83.0 [*C*(CO$_2$Et)$_2$NH], 136.8 [*C*HCH(CO$_2$Et)NH], 162.6 [*C*C(CO$_2$Et)$_2$NH], 168.2, 168.5, 168.6, 170.3 (4 × *C*O$_2$); MS (EI-GC) *m*/*z*: 343 (M^+ + 1, <1%), 270 (20), 226 (10), 198 (100), 170 (30), 166 (20), 152 (65), 126 (25), 122 (10), 120 (50), 94 (12); HRMS calculated for $C_{15}H_{21}NO_8$–$C_3H_5O_2$: 270.0980, found: 270.0995.

(1*R,3*S**,3a*R**,6a*S**)-Diethyl 5-methyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate *endo-cis*-2a.** Sticky yellow oil; R_f 0.14 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2984, 1699, 1595 cm^{-1}; ^1H NMR δ_H: 1.33 (t, *J* = 7.2 Hz, 6H, 2 × $CO_2CH_2CH_3$), 2.94 (s, 3H, NCH_3), 3.57 [m, 2H, 2 × C*H*CH(CO$_2$Et)NH], 3.97 [m, 2H, 2 × C*H*(CO$_2$Et)NH], 4.30 (q, *J* = 7.2 Hz, 4H, 2 × $CO_2CH_2CH_3$), N*H* nd; ^{13}C NMR δ_C: 14.2 (2 × $CO_2CH_2CH_3$), 25.5 (NCH_3), 50.0 [2 × *C*HCH(CO$_2$Et)NH], 61.9 (2 × $CO_2CH_2CH_3$), 63.1 [2 × *C*H(CO$_2$Et)NH], 169.0 (2 × $CO_2CH_2CH_3$), 175.0 (2 × CON); MS (EI-GC) *m*/*z*: 298 (M^+ + 1, 1%), 226 (12), 225 (100), 179 (32), 151 (53), 94 (44), 67 (12); HRMS calculated for $C_{13}H_{18}N_2O_6$: 298.1155, found: 298.1148.

(1*R,3*R**,3a*R**,6a*S**)-Diethyl 5-methyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate *endo-trans*-2a.** Sticky yellow oil; R_f 0.25 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2984, 1774, 1731, 1595 cm^{-1}; ^1H NMR δ_H: 1.33 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.35 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.98 (s, 3H, NCH_3), 3.56 [deform. dd, *J* = 8.0, 8.0 Hz, 1H, C*H*CH(CO$_2$Et)NH], 3.64 [dd, *J* = 8.0, 1.2 Hz, 1H, C*H*CH(CO$_2$Et)NH], 4.13 [d, *J* = 8.0 Hz, 1H, C*H*(CO$_2$Et)NH], 4.24 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.27–4.35 [m, 3H, $CO_2CH_2CH_3$ and C*H*(CO$_2$Et)NH], N*H* nd; ^{13}C NMR δ_C: 14.2, 14.3 (2 × $CO_2CH_2CH_3$), 25.5 (NCH_3), 47.6 [*C*HCH(CO$_2$Et)NH], 48.8 [*C*HCH(CO$_2$Et)NH], 61.8, 62.0 (2 × $CO_2CH_2CH_3$), 62.2 [*C*H(CO$_2$Et)NH], 62.4 [*C*H(CO$_2$Et)NH], 169.7, 171.7 (2 × *C*O$_2$), 175.4, 176.6 (2 × CON); MS (EI-GC) *m*/*z*: 298 (M^+ + 1, 1%), 226 (12), 225 (100), 179 (17), 151 (40), 94 (40), 68 (10), 67 (13); HRMS calculated for $C_{13}H_{18}N_2O_6$: 298.1155, found: 298.1148.

(1*R,3*S**,3a*R**,6a*S**)-Diethyl 5-benzyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate *endo-cis*-2b.** Sticky yellow oil; R_f 0.15 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2984, 1740, 1705 cm^{-1}; ^1H NMR δ_H: 1.28 (t, *J* = 7.1 Hz, 6H, 2 × $CO_2CH_2CH_3$), 3.54 [m, 2H, C*H*CH(CO$_2$Et)NH], 3.94 [m, 2H, C*H*(CO$_2$Et)NH], 4.24 (q, *J* = 7.1 Hz, 4H, 2 × $CO_2CH_2CH_3$), 4.58 (s, 2H, CH_2Ph), 7.18–7.38 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 14.1 (2 × $CO_2CH_2CH_3$), 43.0 (CH_2Ph), 49.8 [2 × *C*HCH(CO$_2$Et)NH], 62.0 (2 × $CO_2CH_2CH_3$), 63.0 [2 × *C*H(CO$_2$Et)NH], 128.1, 128.6, 128.7, 135.2 (Ar*C*), 168.8 (2 × *C*O$_2$CH$_2$CH$_3$), 174.6 (CON); MS (EI-GC) *m*/*z*: 374 (M^+ + 1, 2%), 302 (18), 301 (100), 227 (50), 94 (23), 91 (47), 68 (11); HRMS calculated for $C_{19}H_{22}N_2O_6$: 374.1478, found: 374.1470.

(1*R,3*R**,3a*R**,6a*S**)-Diethyl 5-benzyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate *endo-trans*-2b.** Sticky yellow oil; R_f 0.22 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2990, 1740, 1700 cm^{-1}; ^1H NMR δ_H: 1.23–1.38 (m, 6H, 2 × $CO_2CH_2CH_3$), 3.64 (dd, *J* = 8.0, 1.4 Hz, 1H, C*H*CH(CO$_2$Et)NH), 4.10–4.33 [m, 6H, C*H*CH(CO$_2$Et)NH and C*H*(CO$_2$Et)NH and 2 × $CO_2CH_2CH_3$], 4.52–4.69 (m, 3H, CH_2Ph and C*H*(CO$_2$Et)NH), 7.18–7.40 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 14.2, 14.3 (2 × $CO_2CH_2CH_3$), 43.1 (CH_2Ph), 48.8 [*C*HCH(CO$_2$Et)NH], 49.9 [*C*HCH(CO$_2$Et)NH], 61.8, 62.0 (2 × $CO_2CH_2CH_3$), 62.2 [*C*H(CO$_2$Et)NH], 62.5 [*C*H(CO$_2$Et)NH], 128.1, 128.8, 129.1, 135.4 (Ar*C*), 169.6, 171.7 (2 × *C*O$_2$CH$_2$CH$_3$), 175.0, 176.3 (2 × CON); MS (EI-GC) *m*/*z*: 374 (M^+ + 1, 2%), 302 (18), 301 (100), 227 (31), 94 (20), 91 (44), 68 (13); HRMS calculated for $C_{19}H_{22}N_2O_6$: 374.1478, found: 374.1470.

(1*R,3*S**,3a*R**,6a*S**)-Diethyl 4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate *endo-cis*-2c.** Colorless needles, mp = 123–125 °C (from hexane/$CDCl_3$); R_f 0.11 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2980, 1741, 1732, 1708 cm^{-1}; ^1H NMR δ_H: 1.32 (t, *J* = 7.2 Hz, 6H, 2 × $CO_2CH_2CH_3$), 3.05 (t, *J* = 12.7 Hz, 1H, N*H*), 3.71 [m, 2H, 2 × C*H*CH(CO$_2$Et)NH], 4.06 [m, 2H, C*H*(CO$_2$Et)NH], 4.29 (q, *J* = 7.2 Hz, 4H, 2 × $CO_2CH_2CH_3$), 7.19–7.22 (m, 2H, Ar*H*), 7.37–7.46 (m, 3H, Ar*H*); ^{13}C NMR δ_C: 14.0 (2 × $CO_2CH_2CH_3$), 49.9 [2 × *C*HCH(CO$_2$Et)NH], 62.1 (2 × $CO_2CH_2CH_3$), 63.4 [2 × *C*H(CO$_2$Et)NH], 126.5, 128.9, 129.2, 131.3 (Ar*C*), 169.0 (2 × *C*O$_2$CH$_2$CH$_3$), 174.1 (2 × CON); MS (EI-GC) 360 *m*/*z* (M^+ + 1, 3%), 288 (19), 287 (100), 94 (45), 68 (13), 67 (11); HRMS calculated for $C_{18}H_{20}N_2O_6$: 360.1301, found: 360.1291.

(1*R,3*R**,3a*R**,6a*S**)-Diethyl 4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate *endo-trans*-2c.** Colorless needles, mp = 105–107 °C (from hexane/$CDCl_3$); R_f 0.14 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2976, 1712 cm^{-1}; ^1H NMR δ_H: 1.20–1.32 (m, 6H, 2 × $CO_2CH_2CH_3$), 2.85 (br. s, 1H, N*H*), 3.68 [deform. dd, *J* = 8.1, 8.1 Hz, 1H, C*H*CH(CO$_2$Et)NH], 3.83 [d, *J* = 8.1, 1H, C*H*CH(CO$_2$Et)NH], 4.25 [m, 5H, 2 × $CO_2CH_2CH_3$ and C*H*(CO$_2$Et)NH], 4.42 [s, 1H, C*H*(CO$_2$Et)NH], 7.23–7.27 (m, 2H, Ar*H*), 7.38–7.47 (m, 3H, Ar*H*); ^{13}C NMR δ_C: 14.0, 14.1 (2 × $CO_2CH_2CH_3$), 47.6 [*C*HCH(CO$_2$Et)NH], 49.9 [*C*HCH(CO$_2$Et)NH], 61.9, 62.1 (2 × $CO_2CH_2CH_3$), 62.3 [*C*H(CO$_2$Et)NH], 62.9 [*C*H(CO$_2$Et)NH], 126.4, 128.8, 129.1, 131.5 (Ar*C*), 169.8, 171.4 (2 × *C*O$_2$CH$_2$CH$_3$), 174.6, 175.6 (2 × CON); MS (EI-GC) 360 *m*/*z*: (M^+ + 1, 4%), 67 (10), 68 (13), 94 (40),

287 (100), 288 (17); HRMS calculated for $C_{18}H_{20}N_2O_6$: 360.1301, found: 360.1291.

(1*S,3*R**,3a*S**,6a*R**)-3-Ethyl 1-methyl 1,5-dimethyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate *endo-cis*-3a.** Sticky pale yellow oil; R_f 0.38 (*n*-hexane–ethyl acetate 6 : 4); IR (neat) ν_{max} 2983, 2955, 1777, 1735, 1697 cm^{-1}; ^1H NMR δ_H: 1.36 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.49 [s, 3H, $C(CO_2CH_3)CH_3$], 2.93 (s, 3H, NCH_3), 3.25 [d, *J* = 8.0 Hz, 1H, $CHC(CO_2Me)CH_3$], 3.37 (d, *J* = 12.5 Hz, 1H, NH), 3.63 [deform. dd, *J* = 8.0, 8.0 Hz, 1H, $CHCH(CO_2Et)NH$], 3.83 (s, 3H, CO_2CH_3), 4.14 [dd, *J* = 12.5, 8.0 Hz, 1H, $CH(CO_2Et)NH$], 4.30 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$); ^{13}C NMR δ_C: 14.2 ($CO_2CH_2CH_3$), 24.6 [$C(CO_2CH_3)CH_3$], 25.4 (NCH_3), 50.4 [$CHCH(CO_2Et)NH$], 53.1 [$CHC(CO_2Me)CH_3$], 62.0 (CO_2CH_3), 62.1 ($CO_2CH_2CH_3$), 69.4 [$CH(CO_2Me)CH_3$], 169.5, 171.7 (2 × CO_2), 175.0, 175.2 (2 × CON); MS (EI-GC) *m*/*z*: 298 (M^+ + 1, <1%), 239 (67), 225 (39), 165 (100), 108 (43), 81 (10), 80 (21); HRMS calculated for $C_{13}H_{18}N_2O_6$: 298.1165, found: 298.1163.

(2*R,3*S**,5*S**)-2-Ethyl 3,5-dimethyl 5-methylpyrrolidine-2,3,5-tricarboxylate *endo-cis*-3f.** Yellowish oil; R_f 0.41 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2983, 2954, 1731, 1725, 1700 cm^{-1}; ^1H NMR δ_H: 1.26 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.49 [s, 3H, $C(CO_2CH_3)CH_3$], 2.01 [dd, *J* = 12.9, 9.8 Hz, 1H, $CHHC(CO_2Me)CH_3$], 2.64 [dd, *J* = 12.9, 8.3 Hz, 1H, $CHHC(CO_2Me)CH_3$], 3.19 [ddd, *J* = 9.8, 8.3, 7.1 Hz, 1H, $CH(CO_2Me)$], 3.71, 3.73 (2s, 3H, CO_2CH_3), 3.77 [d, *J* = 7.1 Hz, 1H, $CH(CO_2Et)NH$], 4.16 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$, NH nd; ^{13}C NMR δ_C: 14.3 ($CO_2CH_2CH_3$), 25.9 [$C(CO_2CH_3)CH_3$], 40.7 [$CH_2C(CO_2Me)CH_3$], 47.4 [$CHCH(CO_2Et)NH$], 52.4, 52.7 (2 × CO_2CH_3), 61.6 ($CO_2CH_2CH_3$), 63.0 [$CH(CO_2Et)NH$], 66.3 [$C(CO_2Me)CH_3$], 172.8, 173.5, 176.3 (3 × CO_2); MS (EI-GC) *m*/*z*: 273 (M^+ + 1, <2%), 215 (11), 214 (100), 200 (30), 168 (13), 140 (33), 108 (19), 82 (21); HRMS calculated for $C_{12}H_{19}NO_6$: 273.1212, found: 273.1214.

(2*R,3*S**,5*R**)-2-Ethyl 3,5-dimethyl 5-methylpyrrolidine-2,3,5-tricarboxylate *endo-trans*-3f.** Yellowish oil; R_f 0.22 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2983, 2953, 1732, 1725, 1703 cm^{-1}; ^1H NMR δ_H: 1.25 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.37 [s, 3H, $C(CO_2CH_3)CH_3$], 2.01 [dd, *J* = 13.5, 8.0 Hz, 1H, $CHHC(CO_2Me)CH_3$], 2.68 [dd, *J* = 13.5, 7.2 Hz, 1H, $CHHC(CO_2Me)CH_3$], 3.30 [ddd, *J* = 8.0, 7.2, 7.0 Hz, 1H, $CHCH(CO_2Et)$], 3.62, 3.73 (2s, 3H, CO_2CH_3), 4.03 [d, *J* = 7.0 Hz, 1H, $CH(CO_2Et)NH$], 4.15 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), NH nd; ^{13}C NMR δ_C: 14.2 ($CO_2CH_2CH_3$), 28.3 [$C(CO_2CH_3)CH_3$], 39.1 [$CH_2C(CO_2Me)CH_3$], 47.1 [$CHCH(CO_2Et)NH$], 53.3, 53.4 (2 × CO_2CH_3), 61.4 ($CO_2CH_2CH_3$), 62.8 [$CH(CO_2Et)NH$], 65.4 [$C(CO_2Me)CH_3$], 172.3, 173.6, 176.4 (3 × CO_2); MS (EI-GC) *m*/*z*: 273 (M^+ + 1, <2%), 215 (12), 214 (100), 200 (33), 140 (62), 108 (20), 99 (24), 82 (23); HRMS calculated for $C_{12}H_{19}NO_6$: 273.1212, found: 273.1215.

(2*S,3*R**,5*R**)-5-Ethyl 2,3-dimethyl 2-methylpyrrolidine-2,3,5-tricarboxylate *endo-cis*-3f′.** Yellowish oil; R_f 0.21 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2983, 2955, 1730, 1726, 1700 cm^{-1}; ^1H NMR δ_H: 1.26 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.51 [s, 3H, $C(CO_2CH_3)CH_3$], 2.29–2.57 [m, 2H, $CH_2CH(CO_2Et)$], 2.87 [dd, *J* = 9.5, 8.1 Hz, 1H, $CHC(CO_2Me)CH_3$], 3.65, 3.66 (2s, 3H, CO_2CH_3), 3.87 [dd, *J* = 8.6, 7.6 Hz, 1H, $CH(CO_2Et)NH$], 4.15 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), NH nd; ^{13}C NMR δ_C: 14.3 ($CO_2CH_2CH_3$), 25.5 [$CHC(CO_2Me)CH_3$], 32.3 [$CH_2CH(CO_2Et)NH$], 52.0, 52.1 (2 × CO_2CH_3), 52.5 [$CHC(CO_2Me)Me$], 58.0 [$CH(CO_2Et)NH$], 61.4 ($CO_2CH_2CH_3$), 68.3 [$C(CO_2Me)Me$], 171.6, 172.2, 174.3 (3 × CO_2); MS (EI-GC) *m*/*z*: 273 (M^+ + 1, <2%), 215 (12), 214 (100), 200 (32), 140 (62), 108 (20), 99 (27), 82 (23); HRMS calculated for $C_{12}H_{19}NO_6$: 273.1212, found: 273.1214.

(2*S,3*S**,4*S**,5*R**)-5-Ethyl 2,3,4-trimethyl 2-methylpyrrolidine-2,3,4,5-tetracarboxylate *endo-cis*-3d.** Pale yellow oil; R_f 0.20 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2986, 2954, 2907, 1730, 1729 cm^{-1}; ^1H NMR δ_H: 1.27 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.60 [s, 3H, $C(CO_2CH_3)CH_3$], 3.24 [d, *J* = 10.0 Hz, 1H, $CHC(CO_2Me)Me$], 3.64, 3.68, 3.74 (3s, 3H, CO_2CH_3), 3.78 [dd, *J* = 10.0, 8.1 Hz, 1H, $CHCH(CO_2Et)NH$], 4.02 [d, *J* = 8.1 Hz, 1H, $CH(CO_2Et)NH$], 4.15 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), NH nd; ^{13}C NMR δ_C: 14.2 ($CO_2CH_2CH_3$), 24.9 [$C(CO_2CH_3)CH_3$], 49.6 [$CHC(CO_2Me)Me$], 52.3, 52.6 52.7 (3 × CO_2CH_3), 56.8 [$CHCH(CO_2Et)NH$], 61.7 [$CH(CO_2Et)NH$], 61.8 ($CO_2CH_2CH_3$), 68.4 [$C(CO_2Me)Ph$], 170.6, 172.3, 173.0, 173.8 (4 × CO_2); MS (EI-GC) *m*/*z*: 331 (M^+ + 1, <2%), 272 (65), 258 (19), 262 (19), 241 (10), 240 (82), 226 (99), 212 (80), 198 (60), 180 (10), 167 (11), 166 (100), 154 (25), 140 (72), 139 (10), 136 (10), 122 (10), 108 (58), 94 (11), 81 (22), 80 (27), 59 (24); HRMS calculated for $C_{14}H_{21}NO_8$: 331.1267, found: 331.1274.

(2*R,3*R**,4*R**,5*S**)-5-Ethyl 2-methyl 2-methyl-3,4-bis(phenylsulfonyl)pyrrolidine-2,5-dicarboxylate *endo-cis*-3e.** Orange oil; R_f 0.11 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2985, 2956, 2905, 1735, 1710, 1308, 1146 cm^{-1}; ^1H NMR δ_H: 1.00 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.72 [s, 3H, $C(CO_2CH_3)CH_3$], 3.72 (s, 3H, CO_2CH_3), 3.94 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.27 [d, *J* = 6.5 Hz, 1H, $CH(CO_2Et)NH$], 4.28 [d, *J* = 4.5 Hz, 1H, $CHC(CO_2Me)Me$], 5.01 [dd, *J* = 6.5, 4.5 Hz, 1H, $CHCHCO_2Et$], 7.51–7.71 (m, 6H, ArH), 7.81–8.02 (m, 4H, ArH), NH nd; ^{13}C NMR δ_C: 14.0 ($CO_2CH_2CH_3$), 23.7 [$CHC(CO_2Me)CH_3$], 52.7 [$CH(CO_2Et)NH$], 61.5 (CO_2CH_3), 62.2 ($CO_2CH_2CH_3$), 69.4 [$C(CO_2Me)Me$], 69.5 [$CHC(CO_2Me)Me$], 73.0 [$CHCH(CO_2Et)NH$], 128.4, 128.9, 129.3, 129.4, 134.2, 134.4, 138.1, 140.4 (ArC), 170.1, 171.2 (2 × CO_2); MS (EI-GC) *m*/*z*: 495 (M^+ + 1, <1%), 294 (32), 279 (21), 248 (39), 237 (14), 236 (100), 222 (26), 221 (10), 156 (11), 128 (17), 125 (11), 108 (23), 96 (26), 95 (10), 94 (11), 81 (46), 80 (21), 77 (14); HRMS calculated for $C_{22}H_{25}NO_8S_2$: 495.1022, found: 495.1015.

(1*S,3*R**,3a*S**,6a*R**)-Diethyl 1-benzyl-5-methyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate *endo-cis*-4a.** Sticky pale yellow oil; R_f 0.22 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 3030, 2982, 2936, 1779, 1734, 1699 cm^{-1}; ^1H NMR δ_H: 1.32, 1.34 (2t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.88, 3.30 (2d, *J* = 13.8 Hz, 2H, CH_2Ph), 2.92 (s, 3H, NCH_3), 3.38 [d, *J* = 8.0 Hz, 1H, $CHC(CO_2Et)Bn$], 3.55 [deform. dd, *J* = 8.4, 8.0 Hz, 1H, $CHCH(CO_2Et)NH$], 4.09 [d, *J* = 8.4 Hz, 1H, $CH(CO_2Et)NH$], 4.24 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.26 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), NH nd; ^{13}C NMR δ_C: 14.0 (2 × $CO_2CH_2CH_3$), 25.4 (NCH_3), 42.2 (CH_2Ar), 50.4 [$CHCH(CO_2Et)NH$], 56.6 [$CHC(CO_2Et)Bn$], 62.0 [$CH(CO_2Et)NH$], 62.1 ($CO_2CH_2CH_3$),

62.3 ($CO_2CH_2CH_3$), 73.6 [$C(CO_2Et)Bn$], 127.2, 128.3, 130.4, 135.7 (Ar*C*), 169.6, 170.1 (2 × CO_2), 175.0, 175.1 (2 × CON); MS (EI-GC) *m*/*z*: 388 (M^+ + 1, <1%), 315 (13), 298 (14), 297 (100), 223 (11), 166 (45), 94 (11), 91 (17); HRMS calculated for $C_{20}H_{24}N_2O_6$: 388.1634, found: 388.1631.

(1*S,3*R**,3a*S**,6a*R**)-Diethyl 1,5-dibenzyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate *endo-cis*-4b.** Colorless prisms, mp = 127–130 °C (from hexane/$CDCl_3$); R_f 0.39 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 3030, 2989, 1741, 1719, 1699 cm^{-1}; ^1H NMR δ_H: 1.23 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.28 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.89, 3.31 (2 × d, *J* = 13.9 Hz, 2H, CH_2Ph), 3.38 [d, *J* = 7.8 Hz, 1H, C*H*C(CO$_2$Et)Bn], 3.55 [deform. dd, *J* = 7.8, 7.8 Hz, 1H, C*H*CH(CO$_2$Et)NH], 4.03–4.27 [m, 5H, 2 × $CO_2CH_2CH_3$ and C*H*(CO$_2$Et)NH], 4.54, 4.60 (d, *J* = 14.3 Hz, 2H), 7.20–7.35 (m, 10H, 2 × CH_2Ph), N*H* nd; ^{13}C NMR δ_C: 14.0, 14.1 (2 × $CO_2CH_2CH_3$), 42.2, 43.0 (2 × CH_2Ph), 50.4 [*C*HCH(CO$_2$Et)NH], 56.6 [*C*HCH(CO$_2$Et)NH], 61.9, 62.1 (2 × $CO_2CH_2CH_3$), 62.3 [*C*H(CO$_2$Et)NH], 73.7 [*C*Bn(CO$_2$Et)NH], 127.2, 128.0, 128.3, 128.6, 128.7, 130.5, 135.2, 135.8 (ArC), 169.4, 169.9 (2 × $CO_2CH_2CH_3$), 174.6, 174.7 (2 × CON); MS (EI-GC) *m*/*z*: 464 (M^+ + 1, <1%), 391 (14), 374 (22), 373 (100), 166 (22), 91 (73); HRMS calculated for $C_{26}H_{28}N_2O_6$–C_7H_7: 373.1400, found: 373.1401.

(1*S,3*R**,3a*S**,6a*R**)-Diethyl 1-benzyl-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate *endo-cis*-4c.** Colorless prisms, mp = 169–172 °C (from hexane/$CDCl_3$); R_f 0.34 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2979, 2937, 1729, 1714 cm^{-1}; ^1H NMR δ_H: 1.25–1.30 (m, 6H, 2 × $CO_2CH_2CH_3$), 2.96, 3.36 (2 × d, *J* = 13.9 Hz, 2H, CH_2Ph), 3.51 (s, 1H, N*H*), 3.55 [d, *J* = 7.8 Hz, 1H, C*H*C(CO$_2$Et)Bn], 3.73 [deform. dd, *J* = 7.8, 7.8 Hz, 1H, C*H*CH(CO$_2$Et)NH], 4.15–4.30 [m, 5H, 2 × $CO_2CH_2CH_3$ and C*H*(CO$_2$Et)NH], 7.15–7.49 (m, 10H, Ar*H*); ^{13}C NMR δ_C: 13.9, 14.0 ($CO_2CH_2CH_3$), 42.3 (CH_2Ph), 50.4 [*C*HCH(CO$_2$Et)NH], 56.6 [*C*HCH(CO$_2$Et)NH], 62.1, 62.2 (2 × $CO_2CH_2CH_3$), 62.3 [*C*H(CO$_2$Et)NH], 74.1 [*C*Bn(CO$_2$Et)NH], 126.6, 127.2, 128.0, 128.2, 128.9, 129.2, 130.4, 135.6 (ArC), 169.7, 170.1 (2 × CO_2), 174.0, 174.2 (2 × CON); MS (EI-GC) *m*/*z*: 450 (M^+ + 1, <1%), 377 (14), 360 (22), 359 (100), 207 (44), 166 (40), 156 (10), 119 (10), 94 (13), 91 (45); HRMS calculated for $C_{25}H_{26}N_2O_6$: 450.1791, found: 450.1801.

(2*S,3*S**,4*S**,5*R**)-5-Ethyl 2,3,4-trimethyl 2-benzylpyrrolidine-2,3,4,5-tetracarboxylate *endo-cis*-4d.** Colorless oil; R_f 0.35 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2983, 2954, 2906, 1732, 1727 cm^{-1}; ^1H NMR δ_H: 1.22, 1.26 (2t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 3.13, 3.37 (2d, *J* = 13.8 Hz, 2H, CH_2Ph), 3.34 [d, *J* = 10.1 Hz, 1H, C*H*C(CO$_2$Et)Bn], 3.65 [dd, *J* = 10.1, 8.5 Hz, 1H, C*H*CH(CO$_2$Et)NH], 3.70, 3.78 (2s, 3H, CO_2CH_3), 3.86 [d, *J* = 8.5 Hz, 1H, C*H*(CO$_2$Et)NH], 4.05–4.25 (m, 4H, 2 × $CO_2CH_2CH_3$), 7.24–7.36 (m, 5H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 14.0, 14.2 (2 × $CO_2CH_2CH_3$), 42.6 (CH_2Ar), 49.3 [*C*HC(CO$_2$Et)Bn], 52.4, 52.6 (2 × CO_2CH_3), 54.8 [*C*HCH(CO$_2$Et)NH], 61.6 [*C*H(CO$_2$Et)NH], 62.0, 61.7 (2 × $CO_2CH_2CH_3$), 72.3 [*C*(CO$_2$Et)Bn], 127.1, 128.3, 130.9, 135.9 (Ar*C*), 170.5, 171.9, 172.3, 172.9 (4 × CO_2); MS (EI-GC) *m*/*z*: 407 (M^+ + 1, <1%), 348 (18), 330 (48), 316 (44), 298 (100), 166 (32), 138 (11), 91 (60); HRMS calculated for $C_{20}H_{25}NO_8$: 407.1580, found: 407.1586.

(2*R,3*S**,4*S**,5*S**)-Diethyl 2-benzyl-3,4-bis(phenylsulfonyl)-pyrrolidine-2,5-dicarboxylate *exo-cis*-4e.** Pale yellow prisms, mp = 85–86 °C (from *n*-hexane–ethyl acetate); R_f 0.22 (7 : 3 *n*-hexane–ethyl acetate); IR (neat) ν_{max} 2971, 1741, 1235, 1149 cm^{-1}; ^1H NMR δ_H: 1.04 (t, *J* = 7.2 Hz, 1H, $CO_2CH_2CH_3$), 1.21 (t, *J* = 7.2 Hz, 1H, $CO_2CH_2CH_3$), 3.29, 3.40 (2 × d, *J* = 14.2 Hz, 2H, CH_2Ph), 3.88–4.29 (m, 4H, 2 × $CO_2CH_2CH_3$), 4.20 [C*H*(CO$_2$Et)NH], 4.43 (br. s, 1H, N*H*), 4.51 [d, *J* = 5.2 Hz, 1H, C*H*C(CO$_2$Et)Bn], 4.89 [deform. dd, *J* = 5.2, 5.2 Hz, 1H, C*H*CH(CO$_2$Et)NH], 7.18–7.33 (m, 5H, Ar*H*), 7.44–7.82 (m, 8H, Ar*H*), 7.88–7.98 (m, 2H, Ar*H*); ^{13}C NMR δ_C: 13.8, 14.0 (2 × $CO_2CH_2CH_3$), 41.0 (CH_2Ph), 61.1, 62.2 (2 × $CO_2CH_2CH_3$), 62.3 [*C*HCH(CO$_2$Et)NH], 69.4 [*C*HCBn(CO$_2$Et)NH], 72.0 [*C*H(CO$_2$Et)NH], 73.8 [*C*Bn(CO$_2$Et)NH], 127.4, 128.4, 128.8, 129.1, 129.2, 129.4, 130.7, 134.3, 134.4, 134.7, 138.5, 139.5 (Ar*C*), 169.6, 169.6 (2 × CO_2); MS (EI-GC) *m*/*z*: 585 (M^+ + 1, <1%), 512 (10), 494 (34), 370 (14), 353 (13), 352 (69), 306 (33), 298 (10), 280 (26), 235 (10), 234 (82), 157 (13), 156 (23), 141 (10), 125 (15), 112 (11), 94 (16), 91 (100), 80 (12), 77 (29); HRMS calculated for $C_{29}H_{31}NO_8S_2$–$C_3H_5O_2$: 512.1202, found: 512.1215.

(1*R,3*R**,3a*S**,6a*R**)-3-Ethyl 1-methyl 5-methyl-4,6-dioxo-1-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate *endo-cis*-5a.** Sticky pale yellow oil; R_f 0.21 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2982, 2954, 1779, 1736, 1698 cm^{-1}; ^1H NMR δ_H: 1.25 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.91 (s, 3H, NCH_3), 3.37 [deform. dd, *J* = 8.5, 7.5 Hz, 1H, C*H*CHCO$_2$Et], 3.69 (s, 3H, CO_2CH_3), 3.76 [d, *J* = 8.5, 1H, C*H*(CO$_2$Et)NH], 3.96 [d, *J* = 7.5 Hz, 1H, C*H*(CO$_2$Me)Ph], 4.20 (qd, *J* = 7.2, 1.1 Hz, 2H, $CO_2CH_2CH_3$), 7.22–7.36 (m, 3H, Ar*H*), 7.58–7.63 (m, 2H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 14.2 ($CO_2CH_2CH_3$), 25.5 (NCH_3), 50.3 [*C*HCH(CO$_2$Et)NH], 53.4 [*C*HC(CO$_2$Me)Ph], 56.5 (*C*HCO$_2$Et), 61.6 (CO_2CH_3), 62.1 ($CO_2CH_2CH_3$), 74.8 [*C*(CO$_2$Me)Ph], 127.4, 128.5, 128.7, 138.1 (Ar*C*), 169.6, 170.2 (2 × CO_2), 175.1, 175.4 (2 × CON); MS (EI-GC) *m*/*z*: 360 (M^+ + 1, <1%), 302 (17), 301 (100), 228 (14), 227 (72), 170 (19), 143 (18), 142 (27); HRMS calculated for $C_{18}H_{20}N_2O_6$: 360.1321, found: 360.1322.

(1*S,3*R**,3a*S**,6a*R**)-3-Ethyl 1-methyl 5-methyl-4,6-dioxo-1-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate *endo-trans*-5a.** Sticky pale yellow oil; R_f 0.12 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2983, 2954, 2926, 1781, 1729, 1702 cm^{-1}; ^1H NMR δ_H: 1.39 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.79 (s, 3H, NCH_3), 3.08 (d, *J* = 3.5 Hz, 1H, N*H*), 3.55 [deform. dd, *J* = 7.6, 7.6 Hz, 1H, C*H*CHCO$_2$Et], 3.79 (s, 3H, CO_2CH_3), 3.86 [dd, *J* = 7.6, 3.5 Hz, 1H, C*H*(CO$_2$Et)NH], 4.25 [d, *J* = 7.6 Hz, 1H, C*H*C(CO$_2$Me)Ph], 4.30–4.41 (m, 2H, $CO_2CH_2CH_3$), 7.33–7.41 (m, 3H, Ar*H*), 7.47–7.54 (m, 2H, Ar*H*); ^{13}C NMR δ_C: 14.2 ($CO_2CH_2CH_3$), 25.2 (NCH_3), 45.3 [*C*HCH(CO$_2$Et)NH], 50.4 [*C*HC(CO$_2$Me)Ph], 53.7 (*C*HCO$_2$Et), 59.8 (CO_2CH_3), 61.7 ($CO_2CH_2CH_3$), 74.1 [*C*(CO$_2$Me)Ph], 126.0, 128.5, 128.9, 135.4 (Ar*C*), 169.3, 173.5 (2 × CO_2), 174.1, 175.6 (2 × CON); MS (EI-GC) *m*/*z*: 360 (M^+ + 1, <1%), 302 (18), 301 (100), 228 (13), 227 (63), 170 (20), 143 (22), 142 (30), 115 (15); HRMS calculated for $C_{18}H_{20}N_2O_6$: 360.1321, found: 360.1336.

(2*R,3*R**,5*R**)-5-Ethyl 2,3-dimethyl 2-phenylpyrrolidine-2,3,5-tricarboxylate *endo-cis*-5f.** Yellowish oil; R_f 0.41 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2985, 2953, 1734,

1700 cm^{-1}; ^1H NMR δ_H: 1.29 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.29–2.36 [m, 2H, $CH_2CH(CO_2Et)$], 3.51 [dd, J = 7.6, 4.5 Hz, 1H, $CHC(CO_2Me)Ph$], 3.68, 3.70 (2s, 3H, CO_2CH_3), 3.85 [dd, J = 9.0, 5.7 Hz, 1H, $CH(CO_2Et)NH$], 4.23 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 7.25–7.35 (m, 3H, Ar*H*), 7.73–7.77 (m, 2H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 14.3 ($CO_2CH_2CH_3$), 33.8 [$CH_2CH(CO_2Et)$-NH], 52.2, 52.9 (2 × CO_2CH_3), 54.0 [$CHC(CO_2Me)Ph$], 58.6 [$CH(CO_2Et)NH$], 61.5 ($CO_2CH_2CH_3$), 75.5 [$C(CO_2Me)Ph$], 126.9, 128.1, 128.4, 140.2 (Ar*C*), 172.2, 173.1, 173.6 (3 × CO_2); MS (EI-GC) m/z: 335 (M^+ + 1, <2%), 277 (18), 276 (100), 262 (19), 202 (41), 170 (19), 144 (20), 143 (14), 115 (10), 99 (15); HRMS calculated for $C_{17}H_{21}NO_6$: 335.1369, found: 335.1313.

(2*S,3*R**,5*R**)-5-Ethyl 2,3-dimethyl 2-phenylpyrrolidine-2,3,5-tricarboxylate *endo-trans*-5f.** Yellowish oil; R_f 0.29 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2984, 2953, 1727, 1658 cm^{-1}; ^1H NMR δ_H: 1.30 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.36–2.46 [m, 2H, $CH_2CH(CO_2Et)$], 3.19, 3.72 (2s, 3H, CO_2CH_3), 3.92 [deform. dd, J = 8.0, 7.6 Hz, Ph1H, $CHC(CO_2Me)Ph$], 4.04 [deform. dd, J = 6.5, 5.9 Hz, 1H, $CH(CO_2Et)NH$], 4.26 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 7.24–7.37 (m, 3H, Ar*H*), 7.49–7.53 (m, 2H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 14.3 ($CO_2CH_2CH_3$), 32.7 [$CH_2CH(CO_2Et)$-NH], 50.6, 51.5 (2 × CO_2CH_3), 53.4 [$CHC(CO_2Me)Ph$], 58.5 [CH-$(CO_2Et)NH$], 61.3 ($CO_2CH_2CH_3$), 76.0 [$C(CO_2Me)Ph$], 126.3, 128.3, 128.5, 137.5 (Ar*C*), 172.6, 173.0, 173.9 (3 × CO_2); MS (EI-GC) m/z: 335 (M^+ + 1, <2%), 277 (21), 276 (100), 262 (15), 202 (38), 201 (10), 170 (25), 144 (13), 143 (11), 115 (11), 99 (17); HRMS calculated for $C_{17}H_{21}NO_6$: 335.1369, found: 335.1308.

(2*R,3*S**,4*S**,5*R**)-5-Ethyl 2,3,4-trimethyl 2-phenylpyrrolidine-2,3,4,5-tetracarboxylate *endo-cis*-5d.** Colorless oil; R_f 0.25 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2984, 2954, 1735, 1716, 1713, 1700 cm^{-1}; ^1H NMR δ_H: 1.14 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 3.64, 3.67, 3.75 (3s, 3H, CO_2CH_3), 3.82 [dd, J = 10.1, 8.5 Hz, 1H, $CHCH(CO_2Et)NH$], 3.98 [d, J = 8.5 Hz, 1H, CH-$(CO_2Et)NH$], 4.04 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.38 [d, J = 10.1 Hz, 1H, $CHC(CO_2Me)Ph$], 7.26–7.38 (m, 2H, Ar*H*), 7.51 (dd, J = 8.5, 2.8 Hz, 1H, Ar*H*), 7.70 (dd, J = 8.5, 2.8 Hz, 2H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 14.0 ($CO_2CH_2CH_3$), 51.1, 52.3, 52.6 (3 × CO_2CH_3), 53.3 [$CHC(CO_2Me)Ph$], 53.5 [$CHCH(CO_2Et)NH$], 60.7 [$CH(CO_2Et)NH$], 61.4 ($CO_2CH_2CH_3$), 75.0 [$C(CO_2Me)Ph$], 127.0, 128.1, 128.3, 140.9 (Ar*C*), 170.8, 171.3, 171.7, 172.8 (4 × CO_2); MS (EI-GC) m/z: 393 (M^+ + 1, <2%), 335 (19), 334 (100), 302 (24), 288 (11), 274 (35), 260 (25), 242 (13), 228 (51), 202 (25), 201 (11), 170 (11), 143 (26), 115 (16); HRMS calculated for $C_{19}H_{23}NO_8$: 393.1424, found: 393.1421.

(2*R,3*R**,4*R**,5*R**)-5-Ethyl 2,3,4-trimethyl 2-phenylpyrrolidine-2,3,4,5-tetracarboxylate *exo-cis*-5d.** Colorless oil; R_f 0.30 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2990, 2950, 1748, 1733, 1730, 1715 cm^{-1}; ^1H NMR δ_H: 1.30 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 3.56, 3.69, 3.72 (3s, 3H, CO_2CH_3), 3.64 [deform. dd, J = 6.9, 6.7 Hz, 1H, $CHCH(CO_2Et)NH$], 3.89 [d, J = 6.7 Hz, 1H, $CHC(CO_2Me)Ph$], 4.17 [d, J = 6.9 Hz, 1H, $CH(CO_2Et)NH$], 4.26 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 7.28–7.38 (m, 2H, Ar*H*), 7.51 (dd, J = 7.0, 2.3 Hz, 1H, Ar*H*), 7.70 (dd, J = 7.0, 2.3 Hz, 2H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 14.3 ($CO_2CH_2CH_3$), 51.8, 52.6, 52.8 (3 × CO_2CH_3), 53.6 [$CHC(CO_2Me)Ph$], 54.7 [$CHCH(CO_2Et)NH$], 61.6 [$CH(CO_2Et)NH$], 61.9 ($CO_2CH_2CH_3$), 75.2 [$C(CO_2Me)Ph$], 126.4, 128.1, 128.2, 139.7 (Ar*C*), 171.1, 171.6, 172.0, 172.1 (4 × CO_2); MS (EI-GC) m/z: 393 (M^+ + 1, <1%), 335 (19), 334 (100), 303 (11), 302 (60), 274 (14), 260 (25), 242 (11), 228 (27), 202 (21), 170 (56), 143 (24), 115 (14); HRMS calculated for $C_{19}H_{23}NO_8$: 393.1424, found: 393.1426.

(2*R,3*R**,4*R**,5*S**)-5-Ethyl 2-methyl 2-phenyl-3,4-bis(phenylsulfonyl)pyrrolidine-2,5-dicarboxylate *exo-trans*-5e.** Orange oil; R_f 0.10 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 2981, 2954, 2926, 1738, 1692, 1309, 1147 cm^{-1}; ^1H NMR δ_H: 1.04 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 3.74 (s, 3H, CO_2CH_3), 4.01 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.35 [d, J = 5.0 Hz, 1H, $CH(CO_2Et)NH$], 4.86 [d, J = 5.3 Hz, 1H, $CHC(CO_2Me)Ph$], 4.91 [deform. dd, J = 5.3, 5.0 Hz, 1H, $CHCHCO_2Et$], 7.35–8.05 (m, 15H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 14.0 ($CO_2CH_2CH_3$), 53.2 [$CH(CO_2Et)NH$], 60.9 (CO_2CH_3), 62.3 ($CO_2CH_2CH_3$), 69.4 [$CHCH(CO_2Et)NH$], 74.6 [$CHC(CO_2Me)Ph$], 75.1 [$C(CO_2Me)Ph$], 128.2, 128.3, 128.6, 128.8, 128.9, 129.2, 129.3, 134.0, 134.3, 136.8, 138.6, 140.1 (Ar*C*), 170.0, 170.1 (2 × CO_2); MS (EI-GC) m/z: 557 (M^+ + 1, <1%), 357 (11), 356 (51), 342 (10), 310 (15), 299 (11), 298 (54), 284 (17), 283 (21), 215 (37), 158 (11), 157 (11), 144 (11), 143 (100), 142 (11), 115 (24), 77 (11); HRMS calculated for $C_{27}H_{27}NO_8S_2$: 557.1168, found: 557.1173.

(2*S,5*R**)-3,4,5-Triethyl 2-methyl 2-methyl-2,5-dihydro-1*H*-pyrrole-2,3,4,5-tetracarboxylate *cis*-3g.** Yellowish oil; R_f 0.20 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 3021, 2988, 1732, 1720, 1676, 1619 cm^{-1}; ^1H NMR δ_H: 1.20–1.38 (m, 9H, $CO_2CH_2CH_3$), 1.85 [s, 3H, $C(CO_2CH_3)CH_3$], 3.67 (s, 3H, CO_2CH_3), 4.05–4.35 (m, 7H, $CH(CO_2Et)NH$ and 3 × $CO_2CH_2CH_3$), N*H* nd; ^{13}C NMR δ_C: 14.1, 14.2, 15.4 (3 × $CO_2CH_2CH_3$), 24.9 [$CC(CO_2Me)CH_3$], 53.0 (CO_2CH_3), 61.9 [CH-$(CO_2Et)NH$], 62.1, 62.2, 62.8 (3 × $CO_2CH_2CH_3$), 70.0 [$C(CO_2Me)$-Me], 142.0 [$CC(CO_2Me)Me$], 143.9 [$CCH(CO_2Et)NH$], 168.6, 168.8, 169.3, 169.6 (4 × CO_2); MS (EI-GC) m/z: 357 (M^+ + 1, <5%), 285 (10), 284 (100), 256 (24), 239 (14), 226 (11), 212 (26), 211 (15), 180 (60), 166 (40), 140 (10), 134 (15), 108 (10), 73 (10); HRMS calculated for $C_{16}H_{23}NO_8$: 357.1424, found: 357.1419.

(2*S,5*R**)-3,4,5-Triethyl 2-methyl 2-benzyl-2,5-dihydro-1*H*-pyrrole-2,3,4,5-tetracarboxylate *cis*-4g.** Pale yellow oil; R_f 0.10 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 3030, 2982, 1734, 1728, 1656, 1609 cm^{-1}; ^1H NMR δ_H: 1.20–1.38 (m, 12H, $CO_2CH_2CH_3$), 2.91, 3.09 (2d, J = 13.8 Hz, 2H, CH_2Ph), 3.78 [s, 1H, $CH(CO_2Et)NH$], 4.05–4.30 (m, 8H, $CO_2CH_2CH_3$), 7.24–7.30 (m, 5H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 14.2, 14.3, 14.3, 15.4 (4 × $CO_2CH_2CH_3$), 40.8 (CH_2Ar), 59.5, 61.1, 61.4, 62.0 (4 × $CO_2CH_2CH_3$), 60.7 [$CH(CO_2Et)NH$], 77.1 [$C(CO_2Me)Ph$], 127.0, 128.7, 129.6, 137.1 (Ar*C*), 144.9 [$CCH(CO_2Et)NH$], 145.5[CC-$(CO_2Me)Ph$], 168.2, 168.8, 169.0, 170.6 (4 × CO_2); MS (EI-GC) m/z: 447 (M^+ + 1, <1%), 363 (17), 281 (15), 207 (28), 177 (15), 176 (100), 148 (18), 131 (24), 119 (24), 91 (28), 77 (10); HRMS calculated for $C_{23}H_{29}NO_8$: 447.1893, found: 447.1889.

(2*S,5*R**)-3,4,5-Triethyl 2-methyl 2-phenyl-2,5-dihydro-1*H*-pyrrole-2,3,4,5-tetracarboxylate *cis*-5g.** Colorless oil; R_f 0.11 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 3068, 2925, 1743, 1727, 1656, 1606 cm^{-1}; ^1H NMR δ_H: 1.20, 1.21, 1.28 (3t, J = 7.2 Hz, 9H, 3 × $CO_2CH_2CH_3$), 3.71 (s, 3H, CO_2CH_3), 3.48, 4.13, 4.19 (3 × q, J = 7.2 Hz, 6H, $CO_2CH_2CH_3$), 5.70 [s, 1H,

C*H*(CO_2Et)NH], 7.31–7.37 (m, 5H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 14.0, 14.5, 15.4 (3 × $CO_2CH_2CH_3$), 52.9 (CO_2CH_3), 59.8, 62.1, 66.0 (3 × $CO_2CH_2CH_3$), 60.7 [*C*H(CO_2Et)NH], 77.2 [*C*(CO_2Me)Ph], 127.5, 128.6, 129.1, 137.7 (Ar*C*), 146.0 [*C*CH(CO_2Et)NH], 146.5[*C*C(CO_2Me)Ph], 168.3, 168.8, 169.2, 171.7 (4 × *C*O_2); MS (EI-GC) *m*/*z*: 419 (M^+ + 1, <1%), 342 (10), 277 (18), 276 (100), 249 (21), 202 (10), 171 (10), 170 (38), 77 (11), 73 (10); HRMS calculated for $C_{21}H_{25}NO_8$: 419.1580, found: 495.1596.

Synthesis of aminoalcohols 6 and 7

To a solution of *endo-cis*-**4b** (928 mg, 2 mmol) in DMF (2 ml) was added benzoyl chloride (707 μl, 6 mmol) and Et_3N (278 μl, 2 mmol). After stirring (0.5 h at 25 °C) the resulting suspension was heated at 100 °C for an additional 12 h. Then the DMF was evaporated and dry THF was added.[17] The resulting solution was added into a $LiAlH_4$ suspension (390.6 mg, 10 mmol, 97%) in dry THF. The resulting suspension was stirred for 0.5 h at 25 °C and then refluxed for 12 h. The mixture was cooled at 0 °C and NaOH 10% was added, stirring the emulsion for 30 min. The resulting mixture was filtered off and extracted with ethyl acetate (2 × 8 mL). The organic layer was dried over $MgSO_4$, and the solvent evaporated giving a residue, which was purified by flash chromatography obtaining 215 mg of **6** and 162 mg of **7** (65% overall yield).

(1*R,3*S**,3a*R**,6a*S**)-1,2,5-Tribenzyloctahydropyrrolo[3,4-*c*]pyrrole-1,3-diol 6a.** Sticky oil; R_f 0.45 (ethyl acetate–methanol 9 : 1); IR (neat) ν_{max} 3300, 2923, 1650, 1615 cm^{-1}; ^{1}H NMR δ_H: 2.18–2.26 (m, 2H, C*H*CHCH$_2$OH and C*H*CCH$_2$OH), 2.73–2.87 (2d, *J* = 13.2 Hz, 4H, C*CH*$_2$Ph,), 3.05–3.27 (m, 4H, 2 × C*H*$_2$NBn), 3.30–3.61 [m with 2d at 3.53 and 3.57, *J* = 14.2 Hz, 7H, N*CH*$_2$Ph, 2 × C*H*$_2$OH, C*H*(CH$_2$OH)NBn], 7.15–7.35 (m, 13H, Ar*H*), 7.46–7.52 (m, 2H, Ar*H*), O*H* nd; ^{13}C NMR δ_C: 44.3 (CH_2Ph), 46.0 (*C*HCHCH$_2$OH), 48.3 (*C*HCCH$_2$OH), 52.9 (*C*HCH$_2$OH), 55.1, 57.8 (2 × CH_2NBn), 60.3, 61.5 (2 × N*C*H$_2$Ph), 63.1 (C*C*H$_2$Ph), 64.1, 65.0 (2 × CH_2OH), 126.5, 127.5, 127.6, 128.2, 128.8, 128.9, 129.2, 130.0, 130.6, 135.5, 137.6, 137.9 (Ar*C*); MS (EI-GC) *m*/*z* 442 (M^+ + 1, <1%), 281 (10), 247 (10), 207 (16), 171 (38), 158 (24), 156 (15), 134 (15), 133 (35), 132 (15), 92 (18), 91 (100); microanalysis calculated for $C_{29}H_{34}N_2O_2$: C, 79.0; H, 8.0; N, 6.0%; found: C, 78.6; H, 7.9; N, 6.2%.

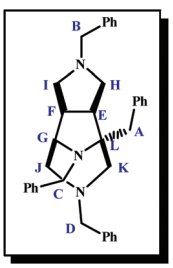
Also product **6** was obtained from **7**. To a solution of **7** (162 mg, 0.46 mmol) in MeCN was added K_2CO_3 (190 mg, 1.40 mmol) and BnBr (54.83 μl, 0.46 mmol). After stirring for 0.5 h at 25 °C the resulting suspension was refluxed for an additional 12 h. Then the solvent was evaporated and the resulting crude was extracted with ethyl acetate (2 × 10 mL) and was washed with brine. After drying over $MgSO_4$, the solvent was evaporated and the residue purified by flash chromatography obtaining 146 mg of **6** (72% yield).

(1*S,3*R**,3a*R**,6a*S**)-1,5-Dibenzyl-1,3-bis(hydroxymethyl) octahydropyrrolo[3,4-*c*]pyrrole 7a.** Sticky oil; R_f 0.33 (ethyl acetate–methanol 9 : 1); IR (neat) ν_{max} 3300, 2923 cm^{-1}; ^{1}H NMR δ_H: 2.27–2.33 and 2.95–3.05 (m, 4H, 2 × C*H*$_2$NBn), 2.62–2.90 (m with 2d at 2.65 and 2.83, *J* = 13.4, 4H, *CH*$_2$Ph, C*H*CHCH$_2$OH, and C*H*CH$_2$OH), 3.44–3.75 (m with 2d at 3.48 and 3.63, *J* = 11.4, 7H, N*CH*$_2$Ph, 2 × C*H*$_2$OH, C*H*CCH$_2$OH), 7.17–7.35 (m, 10H, Ar*H*); ^{13}C NMR δ_C: 44.3 (CH_2Ph), 45.8 (*C*HCHCH$_2$OH), 50.5 (*C*HCH$_2$OH), 54.3, 55.5 (2 × CH_2NBn), 59.7 (*C*HCCH$_2$OH), 60.2 (NC*H*$_2$Ph), 62.4, 64.8 (2 × *C*H$_2$OH), 67.1 [*C*Bn(CH$_2$OH)NH], 127.5, 128.3, 128.5, 128.8, 128.9, 130.5, 137.5, 137.6 (Ar*C*); MS (EI-GC) *m*/*z* 352 (M^+ + 1, <1%), 243 (41), 207 (11), 158 (14), 134 (10), 133 (13), 132 (13), 92 (11), 91 (100), 65 (12); microanalysis calculated for $C_{22}H_{28}N_2O_2$: C, 75.0; H, 8.0; N, 8.0%; found: C, 74.8; H, 8.0; N, 8.3%.

Synthesis of molecule 8

A solution of **6** (120 mg, 0.27 mmol) in dichloromethane was cooled at 0 °C. Then MsCl (21.5 μl, 0.27 mmol, 98%) and Et_3N (38 μl, 0.27 mmol) were added. After stirring for 1 h at 25 °C, the solvent was evaporated and MeCN was added. Then $BnNH_2$ (30 μl, 0.27 mmol, 98%) was added and the resulting solution was refluxed for an additional 15 h. Then the solvent was evaporated and the resulting crude was extracted with ethyl acetate (2 × 8 mL). The organic phase was washed with brine, dried over $MgSO_4$, evaporated *in vacuo*, and the residue purified by flash chromatography obtaining 74 mg of **8** (53% yield).

(3a*S,4*S**,8*R**,8a*R**)-2,4,6,9-Tetrabenzyldecahydro-4,8-epiminopyrrolo[3,4-*d*]azepine (8).** Sticky brown oil; R_f 0.30 (*n*-hexane–ethyl acetate 7 : 3); IR (neat) ν_{max} 3060, 2925, 1669, 1602 cm^{-1}; ^{1}H NMR δ_H: 2.52, 2.72 (2d, *J* = 12.8, 2H, C*CH*$_{2A}$Ph), 2.90–3.05 (m with d at 3.01, *J* = 13.9, 3H, *CH*$_{2K}$, C*H*$_E$ and C*H*$_F$), 3.25–3.41 (m with d at 3.30, *J* = 13.9, 3H, *CH*$_{2K}$, C*H*$_{2J}$ and C*H*$_G$), 3.42–3.70 (4d at 3.47, 3.48, 3.64, 3.65, *J* = 12.9 and 13.0 Hz, 4H, *CH*$_{2B}$Ph and C*H*$_{2D}$Ph), 3.70–4.15 (m, 5H, *CH*$_{2H}$, C*H*$_{2I}$ and C*H*$_{2J}$), 4.30 (s, 2H, *CH*$_{2C}$Ph), 7.15–7.50 (m, 20H, 4 × Ar*H*); ^{13}C NMR δ_C: 40.0 (C_FH), 44.2 (C_KH$_2$), 44.5 (C_EH), 47.2 (C_CH$_2$Ph), 49.9 (C_AH$_2$Ph), 56.5 (C_GH), 60.3, 60.8 (C_BH$_2$Ph and C_DH$_2$Ph), 61.6 (C_JH$_2$), 65.1, 65.4 (C_HH$_2$ and C_IH$_2$), 69.5 (C_L), 127.3, 128.1, 128.2, 128.4, 128.6, 128.7, 128.9, 128.9, 129.5, 130.5, 131.1, 132.2, 134.7, 135.0, 136.4, 137.2 (Ar*C*); MS (EI-GC) *m*/*z* 513 (M^+ + 1, <1%), 195 (17), 194 (17), 106 (100), 105 (23), 104 (49), 132 (13), 92 (20), 91 (94), 79 (28), 78 (15), 77 (29), 65 (18), 51 (17), 43 (10); HRMS calculated for $C_{36}H_{39}N_3$: 513.3144, found: 513.3130.



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