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Silver-catalysed multicomponent 1,3-dipolar cycloaddition of 2-oxoaldehydes-derived azomethine ylides

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Dedicated to Professor Max Malacria on the occasion of his 65th birthday

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ABSTRACT

The silver-catalysed multicomponent reaction between ethyl glyoxylate, 2,2-dimethoxyacetaldehyde, or phenylglyoxal as aldehyde components with a α-amino ester hydrochloride and a dipolarophile in the presence of triethylamine is described. This domino process takes place at room temperature by in situ liberation of the α-amino ester followed by the formation of the imino ester, which is the precursor of a metalloazomethine ylide. The cycloaddition of this species and the corresponding dipolarophile affords polysubstituted proline derivatives. Ethyl glyoxylate reacts with glycinate, alaninate, phenylalaninate and phenylglycinate at room temperature in the presence of representative dipolarophiles affording *endo*-2,5-*cis*-cycloadducts in good yields and high diastereoselection. In addition, 2,2-dimethoxyacetaldehyde is evaluated with the same amino esters and dipolarophiles, under the same mild conditions, generating the corresponding *endo*-2,5-*cis*-cycloadducts with higher diastereoselections than the obtained in the same reactions using ethyl glyoxylate. In the case of phenylglyoxal the corresponding 5-benzoyl-*endo*-2,5-*cis* cycloadducts are obtained in short reaction times and similar diasteroselection.

1. Introduction

Multicomponent process[1]-atom economy[2]-catalysis[3] constitutes three paramount milestones in organic chemistry today. Methodologies involving them constitute a clear trend of innovation in both laboratory and industrial scale. Many reactions do not waste atoms during their whole process, cycloadditions being the most frequently employed.[4] In addition, a large number of domino/multicomponent cycloadditions are found in the literature with very interesting perspectives and applications, especially when a multifunctionalization can be introduced in the final structure. 1,3-Dipolar cycloadditions (1,3-DC)[5,6] involving metalloazomethine ylides and electrophilic alkenes are appropriate to execute this three concepts with high efficiency.[7] With this favourable features, examples of multicomponent 1,3-DC of azomethine ylides are frequently described nowadays.[8,9] Firstly, the 1,3-dipole precursor (normally an imino ester) can be obtained in situ by imine formation from the corresponding aldehyde and the α-amino ester. Second, the metal catalyst fixes the geometry of the dipole favouring a high stereocontrol during the dipolarophile approach and operates under milder reaction conditions. The result of these cycloadditions are polysubstituted pyrrolidines or proline derivatives with an aromatic or heteroaromatic ring at the 5-position, which are very interesting molecules in many scientific areas.[10] In addition, the synthesis of pyrrolizidine alkaloids has been achieved, employ a 1,3-dipolar cycloaddition (1,3-DC) using mainly nitrones[11] or azomethine ylides.[12,13]

In a preliminary work[14] the thermal multicomponent 1,3-DC of diethyl aminomalonate or α-amino esters with ethyl glyoxylate and dipolarophiles could be performed by in situ formation of the imino ester.[14–16] In order to improve the diastereoselectivity, the lowering of the temperature by the employment of metal salts for the enantioselective multicomponent 1,3-DC of imino esters and different dipolarophiles can be achieved.[17] In this work we described the use of silver salts as catalysts for the room temperature multicomponent 1,3-DC of ethyl glyoxylate and also other 2-oxoaldehydes such as 2,2-dimethoxyacetaldehyde and phenylglyoxal for the synthesis of prolinates with different carbonyl groups at the 5-position of the pyrrolidine ring.

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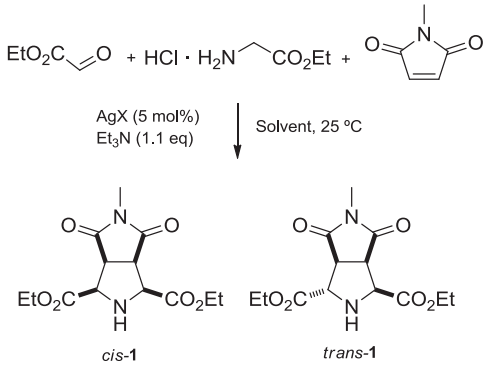
0040-4020/

2. Results and discussion

2.1. 1,3-DC with ethyl glyoxylate

For the optimization studies, ethyl glyoxylate, *N*-methylmaleimide (NMM) and glycine ethyl ester hydrochloride were allowed to react in the presence of triethylamine (1.1 equiv) and silver salt (5 mol %) in toluene at room temperature (Scheme 1, Table 1). The presence of silver salt was crucial because in its absence the reaction failed at room temperature (Table 1, entry 1). When the reaction was performed in toluene, compound **1a** was obtained as a 3:1 *cis*/*trans* pure mixture independently of the silver salt employed (Table 1, entries 2–7). All the silver salts tested such as $AgSbF_6$, AgOTf (OTf=triflate), AgOTfa (OTfa=trifluoroacetate), AgOBz, and Ag_2CO_3 afforded good conversions with very pure crude products. In this sense, AgOAc was selected due to the high conversion achieved (>98%, Table 1, entry 5). The effect of the reaction temperature in the diastereomeric ratio of the product **1a** was also surveyed finding identical *dr* at 25 °C than at 0 °C (Table 1, compare entries 5 and 8). This crude mixture was not so pure when the reaction was run in DCM, THF, Et_2O, or EtOH (Table 1, entries 9–12). Copper(II) perchlorate and triflate can be also used although secondary unidentified products were also formed (Table 1, entries 13 and 14).



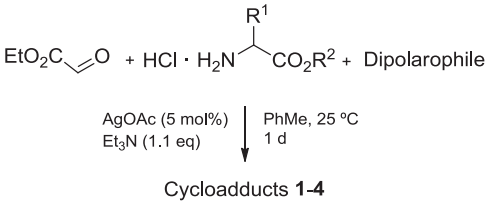
Scheme 1. Optimization of the 1,3-DC between ethyl glycinate, ethyl glyoxylate, and NMM catalysed by silver salts in different solvents.

Table 1
Optimization of the 1,3-DC between ethyl glycinate, ethyl glyoxylate, and NMM catalysed by silver salts[a]

Entry	AgX	Solvent	Conv. (%)[b]	*cis*-1/*trans*-1[c]
1	—	PhMe	<5	—
2	$AgSbF_6$	PhMe	86[d]	3/1
3	AgOTf	PhMe	89[d]	3/1
4	AgOTfa	PhMe	91[d]	3/1
5	AgOAc	PhMe	>98[d]	3/1
6	AgOBz	PhMe	95[d]	3/1
7	Ag_2CO_3	PhMe	95[d]	3/1
8	AgOAc	PhMe[e]	95[d]	3/1
9	AgOAc	DCM	95[f]	3/1
10	AgOAc	THF	92[f]	3/1
11	AgOAc	EtOH	89[f]	2.5/1
12	AgOAc	Et_2O	95[d]	3/1
13	$Cu(ClO_4)_2$	PhMe	90[f]	<3/1
14	$Cu(OTf)_2$	PhMe	90[f]	<3/1

[a] Ethyl glyoxylate (50% w solution in toluene), ethyl aminoglycinate hydrochloride and NMM (1:1:1), triethylamine (1.1 equiv) and the silver salt (5 mol %) were dissolved in toluene and the mixture allowed to react at 25 °C for 19 h.
[b] Obtained by analysis of crude ^{1}H NMR spectra.
[c] Determined by ^{1}H NMR analysis.
[d] Crude product was very pure by ^{1}H NMR.
[e] Reaction performed at 0 °C.
[f] Several impurities were observed by ^{1}H NMR.

With the selected reaction conditions in hand we study the scope of this multicomponent silver-catalysed process starting from ethyl glyoxylate, different maleimides and ethyl glycinate (Scheme 2 and Table 2, entries 1–3). *N*-Benzylmaleimide (NBM) afforded a *cis*/*trans* 3:1 pure mixture of **1b** in excellent yield (Table 2, entry 2). In both examples (NMM and NBM), chemical yields and diastereomeric ratios were higher than under thermal reactions.[14] However, with *N*-phenylmaleimide (NPM) the same diastereomeric ratio in **1c** was identified (*cis*/*trans* 4:1) independently of the thermal or silver-catalysed used method being the chemical yield sensibly higher for the last reaction conditions (Table 2, entry 3). The relative stereochemistry of the stereoisomers **1a**–**c** involving reactions with ethyl glyoxylate was drawn according to the comparison with previously published data (X-ray diffraction analysis and NMR experiments). The control of the geometry of the 1,3-metallodipole by the silver cation is noticeable in this reaction allowing the reaction course through a W,W-shape metallodipole **A**, which afforded 2,5-*cis*-adducts **1** rather than the W,S-shape metallodipole **A** giving 2,5-*trans*-adducts **1** (Scheme 3).



Scheme 2. Silver-catalysed 1,3-DC of α-amino esters and ethyl glyoxylate with dipolarophiles.

Table 2
Scope of the silver catalysed 1,3-DC between ethyl glyoxylate with different α-imino esters and dipolarophiles[a]

Entry	R^1	R^2	Dipolarophile	Product	Yield (%)[b], *dr*[c]
1	H	Et	NMM	*cis*-**1a** / *trans*-**1a**	84, 3/1 (80, 2/1)
2	H	Et	NBM	*cis*-**1b** / *trans*-**1b**	95, 3/1 (64, 1/1)

(*continued on next page*)

Table 2 (*continued*)

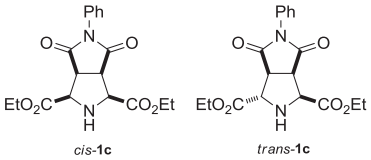
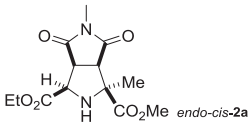
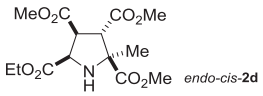
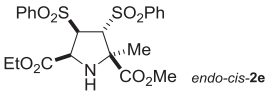
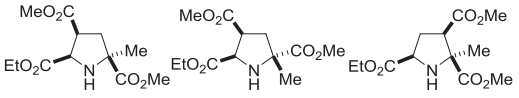
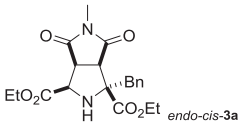
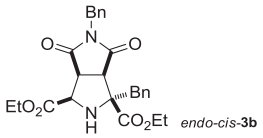
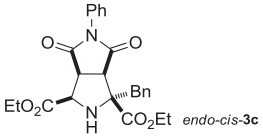
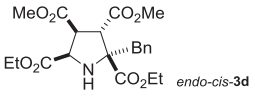
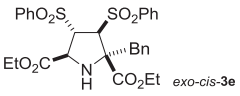
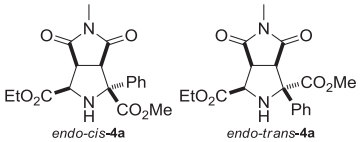
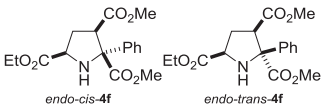
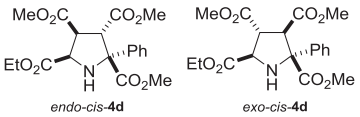
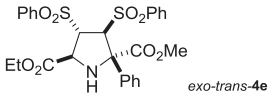
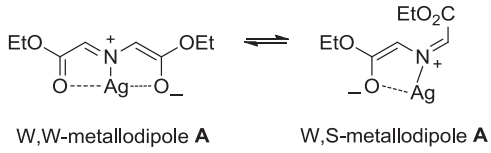
Entry	R^1	R^2	Dipolarophile	Product	Yield (%)[b], *dr*[c]
3	H	Et	NPM	 *cis*-**1c** *trans*-**1c**	85, 4/1 (71, 4/1)
4	Me	Me	NMM	 *endo-cis*-**2a**	59 (85)
5	Me	Me	Dimethyl fumarate	 *endo-cis*-**2d**	55 (70)
6	Me	Me	BPSE[d]	 *endo-cis*-**2e**	65 (66)
7	Me	Me	Methyl acrylate	 *endo-cis*-**2f** *endo-trans*-**2f** *endo-cis*-**2f'**	53, 1/1/1.5 (60, 1/1/1.5)
8	Bn	Et	NMM	 *endo-cis*-**3a**	83 (96)
9	Bn	Et	NBM	 *endo-cis*-**3b**	68 (75)
10	Bn	Et	NPM	 *endo-cis*-**3c**	85 (80)
11	Bn	Et	Dimethyl fumarate	 *endo-cis*-**3d**	38 (80)
12	Bn	Et	BPSE[d]	 *exo-cis*-**3e**	48 (60)
13	Ph	Me	NMM	 *endo-cis*-**4a** *endo-trans*-**4a**	90, 2.5/1 (87, 2/1)
14	Ph	Me	Methyl acrylate	 *endo-cis*-**4f** *endo-trans*-**4f**	45, 2/1 (67, 1/1)

Table 2 (*continued*)

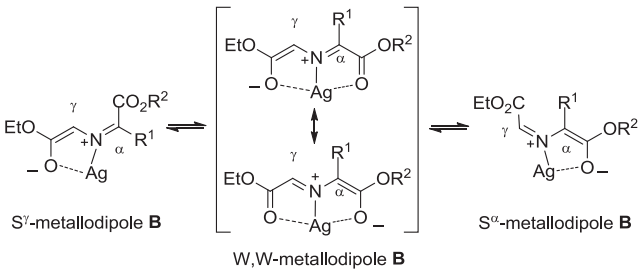
Entry	R^1	R^2	Dipolarophile	Product	Yield (%)[b], *dr*[c]
15	Ph	Me	Dimethyl fumarate	 *endo-cis*-**4d** *exo-cis*-**4d**	45, 2/3 (87, 1/1)
16	Ph	Me	BPSE[d]	 *exo-trans*-**4e**	25 (68)

[a] Ethyl glyoxylate (50% w solution in toluene), amino ester hydrochloride and the dipolarophile (1:1:1), triethylamine (1.1 equiv) and the silver salt (5 mol %) were dissolved in toluene and the mixture allowed to react at 25 °C for 1 d.
[b] Isolated yield after column chromatography.
[c] In brackets data of the process performed under thermal conditions (Ref. 14).
[d] BDSE 1,2-bis(phenylsulfonyl)ethylene.



Scheme 3. Metallodipole conformations derived from glycine ethyl ester and ethyl glyoxylate.

Due to the importance of the quaternary α-amino acids in many scientific areas, the multicomponent 1,3-DC employing several α-substituted α-amino esters were tested. When alanine methyl ester hydrochloride was allowed to react with ethyl glyoxylate and NMM under the optimized reaction conditions *endo-cis*-cycloadduct **2a** was isolated in 59% yield as unique diastereoisomer with lower yield than the obtained in the thermal process[14] (Scheme 2, Table 2, entry 4). No difference was observed in the reactions (thermal[14] or silver-catalysed) involving methyl acrylate, dimethyl fumarate, and 1,2-bis(phenylsulfonyl)ethylene (Scheme 2, Table 2, entries 5–7). The diastereoselective transformation occurred for both (*E*)-configured alkenes furnishing *endo-cis*-**2d** and *endo-cis*-**2e** in 55 and 65% yields, respectively (Table 2, entries 5 and 6). A mixture of three stereoisomers (*cis*- and *trans*-**2f** and **2f′**) was obtained in 45% yield in the case of methyl acrylate and alanine methyl ester hydrochloride (Scheme 2, Table 2, entry 7). According to these results W,W-shape metallodipole **B** (Scheme 4) is mainly originated by the silver cation. We can assume that the preferred attack occurred through the less hindered γ-position when methyl acrylate was employed as dipolarophile.



Scheme 4. Metallodipole conformations derived from α-substituted amino esters and ethyl glyoxylate.

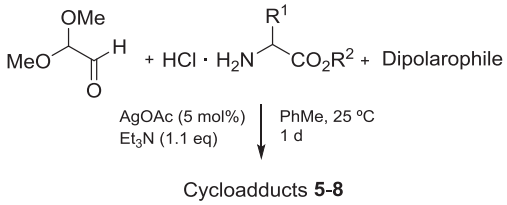
Phenylalanine ethyl ester hydrochloride smoothly reacted with maleimides at room temperature using ethyl glyoxylate and silver acetate (5 mol %). Again, *endo-cis* cycloadducts **3a**–**c** were isolated diastereoselectively in good chemical yields (Scheme 2, Table 2, entries 8–10). However, when more sterically hindered dimethyl fumarate and 1,2-bis(phenylsulfonyl)ethylene (BPSE) were employed as dipolarophiles, lower chemical yields were obtained than under thermal conditions. The reaction was diastereoselective affording *exo-cis*-cycloadduct **3d** and *endo-cis*-cycloadduct **3e**, respectively (Scheme 2, Table 2, entries 11 and 12). With all this information W,W-shape type metallodipole **B** (Scheme 4) should be mainly generated during the reaction course employing the phenylalaninate.

In the case of phenylglycine methyl ester, the major *endo-cis* compound **4a** was obtained through a W,W-shape metallodipole **B** geometry (Scheme 4). The chemical yield of the reaction carried out with methyl acrylate was 45% affording a 1:1 mixture of the *cis*- and *trans*-adducts **4f**, which demonstrated a higher proportion of the S^{γ}-shape metallodipole **B** during the reaction course (Schemes 2 and 4, Table 2, entry 14). In both examples, the diastereomeric ratio was slightly higher than the originally reported for the analogous thermal processes[14] 2.5:1 versus 2:1 and 2:1 versus 1:1, respectively. *E*-1,2-Disubstituted electrophilic alkenes were not very appropriate substrates for the cycloaddition using silver-catalysed conditions. In both diastereoselective transformations chemical yields were lower than the results obtained for the thermal processes.[14] The *exo*-adducts **4d** and **4e** predominated (Scheme 2, Table 2, entries 15 and 16). The bulkier phenylsulfonyl group, presumably preferred to react through the S-shape metallodipoles **B** rather than W-shaped one (Scheme 4).

We anticipate that working with different ester groups at 2- and 5- positions as occurred in final α-substituted prolines **2**, and **4** would allow to transform chemoselectively one of them (less sterically hindered) leaving the other ester group unaltered.

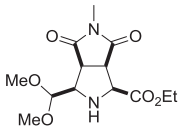
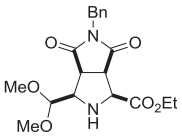
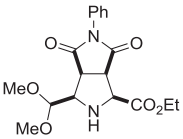
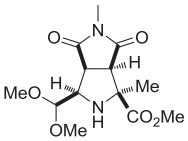
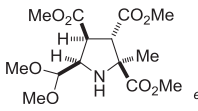
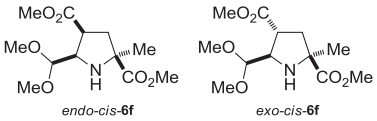
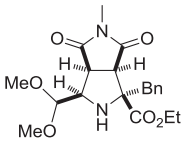
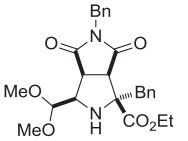
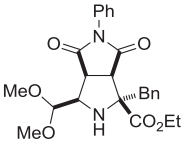
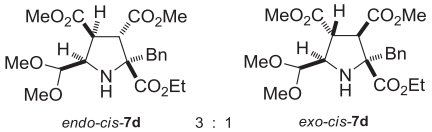
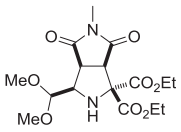
2.2. 1,3-DC with 2,2-dimethoxyacetaldehyde

Following the same strategy and with the idea to introduce a new protected formyl group at the 5-position of the pyrrolidine ring, we next evaluated the scope of the multicomponent process using 2,2-dimethoxyacetaldehyde as imine precursor. Ethyl glycinate, maleimides and 2,2-dimethoxyacetaldehyde was an appropriate combination to be catalysed by AgOAc (Scheme 5 and Table 3). Again the presence of the silver salt was crucial for



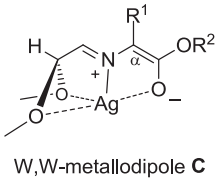
Scheme 5. Silver-catalysed 1,3-DC of α-amino esters and 2,2-dimethoxyacetaldehyde with dipolarophiles.

Table 3
Scope of the silver catalysed 1,3-DC between 2,2-dimethoxyacetaldehyde with different α-imino esters and dipolarophiles[a]

Entry	R^1	R^2	Dipolarophile	Product	Yield (%)[b]
1	H	Et	NMM	 *endo-cis*-**5a**	74[c,d]
2	H	Et	NBM	 *endo-cis*-**5b**	73[d]
3	H	Et	NPM	 *endo-cis*-**5c**	71[d]
4	Me	Me	NMM	 *endo-cis*-**6a**	89[d]
5	Me	Me	Dimethyl fumarate	 *endo-cis*-**6d**	43[d]
6	Me	Me	Methyl acrylate	 *endo-cis*-**6f** 1 : 1 *exo-cis*-**6f**	85
7	Bn	Et	NMM	 *endo-cis*-**7a**	87[d]
8	Bn	Et	NBM	 *endo-cis*-**7b**	96[d]
9	Bn	Et	NPM	 *endo-cis*-**7c**	85[d]
10	Bn	Et	Dimethyl fumarate	 *endo-cis*-**7d** 3 : 1 *exo-cis*-**7d**	66
11	CO_2Et	Et	NMM	 *all-cis*-**8**	70[d]

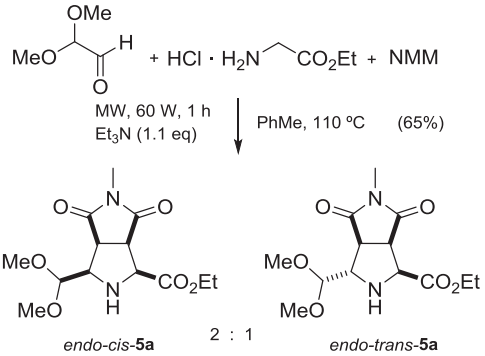
[a] 2,2-Dimethoxyacetaldehyde, amino ester hydrochloride and the dipolarophile (1:1:1), triethylamine (1.1 equiv) and the silver salt (5 mol %) were dissolved in toluene and the mixture allowed to react at 25 °C for 1 d.
[b] Isolated yield after column chromatography.
[c] Thermal MW-reaction afforded a 2:1 mixture of diastereoisomers (see text).
[d] *dr*>50:1, determined by ^{1}H NMR analysis.

obtaining total reaction conversions. In general, the reaction was diastereoselective (>50:1 ratio by ^{1}H NMR) and the chemical yields of *endo*-2,5-*cis*-adducts **5** were satisfactory (71–74%) (Scheme 5, Table 3, entries 1–3). These results indicated that stabilization of the W,W-shape metallodipole type-**C** during the reaction course is very important, probably due to a stronger coordination between the two methoxy groups rather than the carbonyl group of the glyoxylate (Scheme 6). The unfruitful multicomponent reaction of acetaldehyde, glycine methyl ester hydrochloride and NMM confirmed the important role of this extra-coordination of dipole **C**.

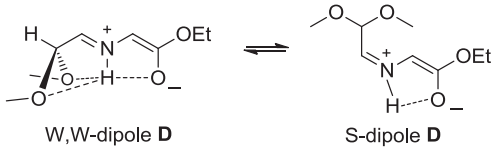


Scheme 6. Metallodipole conformation derived from 1,3-DC of α-substituted amino esters and 2,2-dimethoxyacetaldehyde.

In addition, the microwave-assisted reaction at 110 °C was performed using NMM as example. This thermal transformation produced a 2:1 mixture of *cis*:*trans endo*-cycloadducts **5a** in 65% yield (Scheme 7). In this last example, the thermal [1,2]-prototropy did not control the geometry of the dipole as expected due to the existence of S-dipole **D** in high proportions (Scheme 8). The contrast of this low diastereoselection with the good result achieved in the silver-catalysed process prompted us to discard a parallel study of the thermal reaction conditions.



Scheme 7. Thermal 1,3-DC of ethyl glycinate, NMM and 2,2-dimethoxyacetaldehyde.



Scheme 8. Dipole conformation for thermal 1,3-DC of ethyl glycinate, NMM and 2,2-dimethoxyacetaldehyde.

Almost complete diastereoselection was detected when alanine derivative and 2,2-dimethoxyacetaldehyde were allowed to react with NMM and dimethyl fumarate. Compound *endo*-2,5-*cis*-**6a** was isolated in 89% yield whilst *endo*-2,5-*cis*-**6d** was obtained in a lower 43% yield (Scheme 5, Table 3, entries 4 and 5). In this last reaction, apart from starting reagents, small amounts of other secondary products were hardly detected. When methyl acrylate was tested as dipolarophile an equimolar mixture of *endo*-2,5-*cis*- and *exo*-2,5-*cis*-stereoisomers **6f**, together with an unidentified diastereoisomer was obtained. Stereoisomers **6f** were isolated after purification in 85% yield (Scheme 5, Table 3, entry 6).

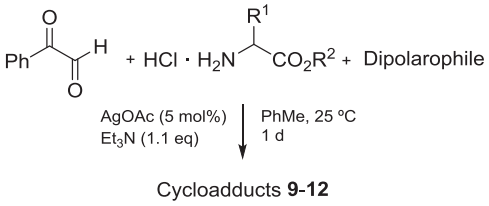
Phenylalanine ethyl ester derivative afforded *endo*-*cis*-compounds **7a**–**c** in very good chemical yields and excellent diastereoselections upon domino reaction with a maleimide and 2,2-dimethoxyacetaldehyde (Scheme 5, Table 3, 7–9). The crude reaction ^{1}H NMR spectra revealed that any other stereoisomer was formed.

Besides, a considerable lower diastereoselection was obtained when dimethyl fumarate was employed as dipolarophile. The 3:1 *endo*-*cis*-**7d**:*exo*-*cis*-**7d** ratio was determined by ^{1}H NMR and the relative configuration assigned according to NOE experiments (Scheme 5, entry 10). At this point the reaction with 1,2-bis(phenylsulfonyl)ethylene completely failed, which confirms the low chemical yield observed in precedent reactions possibly due to steric reasons. The reactions dealing with phenylglycine derivative were surveyed obtaining very complex crude reaction products with many side products.

Unlike the behaviour observed with ethyl glyoxylate, 2,2-dimethoxyacetaldehyde reacted in the presence of NMM and diethyl aminomalonate in good yield (70%) and high diastereomeric ratio affording mainly *all-cis* compound **8** (Scheme 5, Table 3, entry 11).

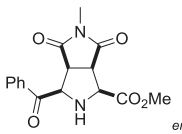
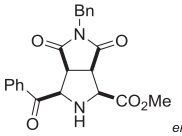
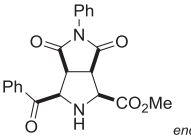
2.3. 1,3-DC with phenylglyoxal

The benzoyl group was introduced at the 5-position of the pyrrolidine ring by employing phenylglyoxal as aldehyde component.[16] The reactions were carried out under identical conditions described in the two previous sections, silver salt being necessary for the success of the process (Scheme 9 and Table 4).



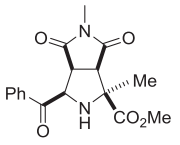
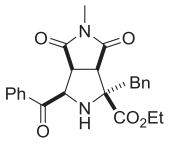
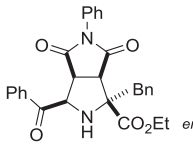
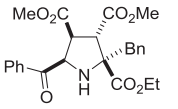
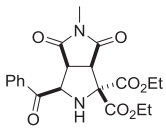
Scheme 9. Silver-catalysed 1,3-DC of α-amino esters and phenylglyoxal with dipolarophiles.

Table 4
Scope of the silver catalysed 1,3-DC between phenylglyoxal with different α-imino esters and dipolarophiles[a]

Entry	R^1	R^2	Dipolarophile	Product	Yield (%)[b]
1	H	Me	NMM	 *endo-cis*-**9a**	55[c]
2	H	Me	NBM	 *endo-cis*-**9b**	48
3	H	Mr	NPM	 *endo-cis*-**9c**	70

(*continued on next page*)

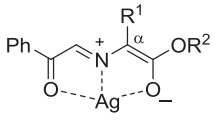
Table 4 (*continued*)

Entry	R^1	R^2	Dipolarophile	Product	Yield (%)[b]
4	Me	Me	Maleimide	 *endo-cis*-**10a**	64
5	Bn	Et	NMM	 *endo-cis*-**11a**	78
6	Bn	Et	NPM	 *endo-cis*-**11c**	97
7	Bn	Et	Dimethyl fumarate	 *endo-cis*-**11d**	47
8	CO_2Et	Et	NMM	 *all-cis*-**12**	40

[a] Phenylglyoxal, amino ester hydrochloride and the dipolarophile (1:1:1), triethylamine (1.1 equiv) and the silver salt (5 mol %) were dissolved in toluene and the mixture allowed to react at 25 °C for 1 d.
[b] Isolated yield after column chromatography.
[c] A small amount (5%) of *exo-cis*-**9a** was isolated.

The reactions involving glycine methyl ester hydrochloride and maleimides afforded cycloadducts *endo*-2,5-*cis*-**9** in moderate to good chemical yields (Table 4, entries 1–3). Alanine or phenylalanine derivatives and maleimides also gave the expected 2,5-*cis*-products **10a**, **11a** and **11c**, in good yields and excellent *endo*-diastereoselection (Table 4, entries 4–6). Methyl fumarate reacted in the presence of the phenylalanine giving compound **11d** as unique stereoisomer in 47% yield. The multicomponent reaction of NMM and diethyl aminomalonate occurred in moderate yield (40%) and high diastereomeric ratio affording mainly *all-cis* compound **12** (Scheme 9, Table 4, entry 8). In some examples we observed a slight decomposition of the cycloadducts during the chromatographic separation and a deactivation of flash silica-gel was previously done with triethylamine.

The intermediacy of the W,W-metallodipole **F** as intermediate species (Fig. 1) can justify the relative *cis*-configuration between two and five substituents.



W,W-metallodipole **F**

Fig. 1. Metallodipole conformations derived from α-substituted amino esters and phenylglyoxal.

3. Conclusions

The silver catalysed *endo*-diastereoselective multicomponent 1,3-DC using α-amino esters, dipolarophiles and functionalized aldehydes such as ethyl glyoxylate, 2,2-dimethoxyacetaldehyde, or phenylglyoxal was successfully accomplished. In general, in the catalysed process with ethyl glyoxylate the *endo*-2,5-*cis*-diastereoselections and chemical yields were in general better than those obtained under thermal conditions. When the reaction was performed with 2,2-dimethoxyacetaldehyde or phenylglyoxal the silver-catalysed conditions for the cycloaddition gave the best results. In this case, higher 2,5-*cis*-diastereoselections than in the reactions involving ethyl glyoxylate were obtained, possibly due to the most favoured W,W-metallodipole geometry.

4. Experimental section

4.1. General

The structurally most important peaks of the IR spectra (recorded using a Nicolet 510 P-FT) 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 solvent and TMS as 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. 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, Merck silica gel 60 (0.040–0.063 mm) was employed.

4.2. General procedure for the synthesis of cycloadducts

Ethyl glyoxylate (100 μL, 0.5 mmol, 50% in toluene) or 2,2-dimethoxyacetaldehyde (75 μL, 0.5 mmol, 50% in water), or phenylglyoxal monohydrate (58 μL, 0.5 mmol); diethyl aminomalonate hydrochloride or the amino acid ethyl ester hydrochloride (0.5 mmol), the corresponding dipolarophile (0.5 mmol), AgOAc (4.1 mg, 0.025 mmol) and triethylamine (90 μL, 0.55 mmol) were dissolved in toluene (4 mL). The reaction vessel was covered with an aluminium foil in order to prevent the light exposure. Once the reaction was judged complete after a TLC test 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. The reaction involving ethyl glyoxylate and 2,2-dimethoxyacetaldehyde were scaled up 10 times to afford *endo-cis*-**3a** and *endo-cis*-**5a** in 80% and 75%, respectively.

4.2.1. Diethyl (1R,3S*,3aR*,6aS*)-5-methyl-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1,3-dicarboxylate (endo-cis-**1a**).*[14] Sticky yellow oil; IR (neat) ν_{max} 2984, 1699, 1595 cm^{-1}; ^{1}H 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×*CH*CH(CO_2Et)NH], 3.97 [m, 2H, 2×*CH*(CO_2Et)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_2Et)NH], 61.9 (2×$CO_2CH_2CH_3$), 63.1 [2×*C*H(CO_2Et)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 calcd for $C_{13}H_{18}N_2O_6$: 298.1155, found: 298.1148.

4.2.2. Diethyl (1R,3R*,3aR*,6aS*)-5-methyl-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1,3-dicarboxylate (endo-trans-**1a**).*[14] Sticky yellow oil; IR (neat) ν_{max} 2984, 1774, 1731, 1595 cm^{-1}; ^{1}H 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, *CH*CH(CO_2Et)NH], 3.64 [dd, *J*=8.0, 1.2 Hz, 1H, *CH*CH(CO_2Et)NH], 4.13 [d, *J*=8.0 Hz, 1H,

C*H*(CO_2Et)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_2Et)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_2Et)NH], 48.8 [*C*HCH(CO_2Et)NH], 61.8, 62.0 (2×$CO_2CH_2CH_3$), 62.2 [*C*H(CO_2Et)NH], 62.4 [*C*H(CO_2Et)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 calcd for $C_{13}H_{18}N_2O_6$: 298.1155, found: 298.1148.

4.2.3. Diethyl (1R,3S*,3aR*,6aS*)-5-benzyl-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1,3-dicarboxylate (endo-cis-**1b**).*[14] Sticky yellow oil; IR (neat) ν_{max} 2984, 1740, 1705 cm^{-1}; ^{1}H NMR δ_H: 1.28 (t, *J*=7.1 Hz, 6H, 2×$CO_2CH_2CH_3$), 3.54 [m, 2H, C*H*CH(CO_2Et)NH], 3.94 [m, 2H, C*H*(CO_2Et)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×CHCH(CO_2Et)NH], 62.0 (2×$CO_2CH_2CH_3$), 63.0 [2×CH(CO_2Et)NH], 128.1, 128.6, 128.7, 135.2 (Ar*C*), 168.8 (2×*C*$O_2CH_2CH_3$), 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 calcd for $C_{19}H_{22}N_2O_6$: 374.1478, found: 374.1470.

4.2.4. Diethyl (1R,3R*,3aR*,6aS*)-5-benzyl-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1,3-dicarboxylate (endo-trans-**1b**).*[14] Sticky yellow oil; IR (neat) ν_{max} 2990, 1740, 1700 cm^{-1}; ^{1}H 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_2Et) NH), 4.10–4.33 [m, 6H, C*H*CH(CO_2Et)NH and C*H*(CO_2Et)NH and 2×$CO_2CH_2CH_3$], 4.52–4.69 (m, 3H, CH_2Ph and C*H*(CO_2Et)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 [CHCH(CO_2Et)NH], 49.9 [CHCH(CO_2Et)NH], 61.8, 62.0 (2×$CO_2CH_2CH_3$), 62.2 [CH(CO_2Et)NH], 62.5 [*C*H(CO_2Et)NH], 128.1, 128.8, 129.1, 135.4 (Ar*C*), 169.6, 171.7 (2×*C*$O_2CH_2CH_3$), 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 calcd for $C_{19}H_{22}N_2O_6$: 374.1478, found: 374.1470.

4.2.5. Diethyl (1R,3S*,3aR*,6aS*)-4,6-dioxo-5-phenyloctahydro pyrrolo[3,4-c]pyrrole-1,3-dicarboxylate (endo-cis-**1c**).*[14] Colourless needles, mp=123–125 °C (from hexane/$CDCl_3$); IR (neat) ν_{max} 2980, 1741, 1732, 1708 cm^{-1}; ^{1}H 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_2Et)NH], 4.06 [m, 2H, C*H*(CO_2Et)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×CHCH(CO_2Et)NH], 62.1 (2×$CO_2CH_2CH_3$), 63.4 [2×CH(CO_2Et)NH], 126.5, 128.9, 129.2, 131.3 (Ar*C*), 169.0 (2×*C*$O_2CH_2CH_3$), 174.1 (2×CON); MS (EI-GC) 360 *m/z* (M^++1, 3%), 288 (19), 287 (100), 94 (45), 68 (13), 67 (11); HRMS calcd for $C_{18}H_{20}N_2O_6$: 360.1301, found: 360.1291.

4.2.6. Diethyl (1R,3R*,3aR*,6aS*)-4,6-dioxo-5-phenyloctahydro pyrrolo[3,4-c]pyrrole-1,3-dicarboxylate endo-trans-**1c**).*[14] Colourless needles mp=105–107 °C (from hexane/$CDCl_3$); IR (neat) ν_{max} 2976, 1712 cm^{-1}; ^{1}H 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_2Et)NH], 3.83 [d, *J*=8.1, 1H, C*H*CH(CO_2Et)NH], 4.25 [m, 5H, 2×$CO_2CH_2CH_3$ and C*H*(CO_2Et)NH], 4.42 [s, 1H, C*H*(CO_2Et)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_2Et)NH], 49.9 [*C*HCH(CO_2Et)NH], 61.9, 62.1 (2×$CO_2CH_2CH_3$), 62.3 [*C*H(CO_2Et)NH], 62.9 [*C*H(CO_2Et)NH], 126.4, 128.8, 129.1, 131.5 (Ar*C*), 169.8, 171.4 (2×*C*$O_2CH_2CH_3$), 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 calcd for $C_{18}H_{20}N_2O_6$: 360.1301, found: 360.1291.

4.2.7. 3-Ethyl 1-methyl (1S,3R*,3aS*,6aR*)-1,5-dimethyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1,3-dicarboxylate endo-cis-**2a**).*[14] Sticky pale yellow oil; IR (neat) ν_{max} 2983, 2955, 1777, 1735, 1697 cm^{-1}; ^{1}H NMR δ_H: 1.36 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.49 [s, 3H, C(CO_2CH_3)C*H*$_3$], 2.93 (s, 3H, NC*H*$_3$), 3.25 [d, *J*=8.0 Hz, 1H, C*H*C(CO_2Me)CH_3], 3.37 (d, *J*=12.5 Hz, 1H, N*H*), 3.63 [deform. dd, *J*=8.0, 8.0 Hz, 1H, C*H*CH(CO_2Et)NH], 3.83 (s, 3H, CO_2CH_3), 4.14 [dd, *J*=12.5, 8.0 Hz, 1H, C*H*(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 [*C*HC(CO_2Me)CH_3], 62.0 (CO_2CH_3), 62.1 ($CO_2CH_2CH_3$), 69.4 [*C*H(CO_2Me)CH_3], 169.5, 171.7 (2×*C*O_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 calcd for $C_{13}H_{18}N_2O_6$: 298.1165, found: 298.1163.

4.2.8. 5-Ethyl 2,3,4-trimethyl (2S,3S*,4S*,5R*)-2-methylpyrrolidine-2,3,4,5-tetracarboxylate (endo-cis-**2d**).*[14] Pale yellow oil; IR (neat) ν_{max} 2986, 2954, 2907, 1730, 1729 cm^{-1}; ^{1}H NMR δ_H: 1.27 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.60 [s, 3H, C(CO_2CH_3)C*H*$_3$], 3.24 [d, *J*=10.0 Hz, 1H, C*H*C(CO_2Me)Me], 3.64, 3.68, 3.74 (3s, 3H, CO_2CH_3), 3.78 [dd, *J*=10.0, 8.1 Hz, 1H, C*H*CH(CO_2Et)NH], 4.02 [d, *J*=8.1 Hz, 1H, C*H*(CO_2Et)NH], 4.15 (q, *J*=7.1 Hz, 2H, $CO_2CH_2CH_3$), N*H* 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×*C*O_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 calcd for $C_{14}H_{21}NO_8$: 331.1267, found: 331.1274.

4.2.9. 5-Ethyl 2-methyl (2R,3R*,4R*,5S*)-2-methyl-3,4-bis(phenylsulfonyl)pyrrolidine-2,5-dicarboxylate (endo-cis-**2e**).*[14] Orange oil; IR (neat) ν_{max} 2985, 2956, 2905, 1735, 1710, 1308, 1146 cm^{-1}; ^{1}H NMR δ_H: 1.00 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.72 [s, 3H, C(CO_2CH_3)C*H*$_3$], 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, C*H*(CO_2Et)NH], 4.28 [d, *J*=4.5 Hz, 1H, C*H*C(CO_2Me)Me], 5.01 [dd, *J*=6.5, 4.5 Hz, 1H, C*H*CHCO_2Et], 7.51–7.71 (m, 6H, Ar*H*), 7.81–8.02 (m, 4H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 14.0 ($CO_2CH_2CH_3$), 23.7 [CHC(CO_2Me)*C*H$_3$], 52.7 [*C*H(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 [*C*HCH(CO_2Et)NH], 128.4, 128.9, 129.3, 129.4, 134.2, 134.4, 138.1, 140.4 (Ar*C*), 170.1, 171.2 (2×*C*O_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 calcd for $C_{22}H_{25}NO_8S_2$: 495.1022, found: 495.1015.

4.2.10. 2-Ethyl 3,5-dimethyl (2R,3S*,5S*)-5-methylpyrrolidine-2,3,5-tricarboxylate (endo-cis-**2f**).*[14] Yellowish oil; IR (neat) ν_{max} 2983, 2954, 1731, 1725, 1700 cm^{-1}; ^{1}H NMR δ_H: 1.26 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.49 [s, 3H, C(CO_2CH_3)C*H*$_3$], 2.01 [dd, *J*=12.9, 9.8 Hz, 1H, C*H*HC(CO_2Me)CH_3], 2.64 [dd, *J*=12.9, 8.3 Hz, 1H, C*H*HC(CO_2Me)CH_3], 3.19 [ddd, *J*=9.8, 8.3, 7.1 Hz, 1H, C*H*(CO_2Me)], 3.71, 3.73 (2s, 3H, CO_2CH_3), 3.77 [d, *J*=7.1 Hz, 1H, C*H*(CO_2Et)NH], 4.16 (q, *J*=7.2 Hz, 2H, $CO_2CH_2CH_3$), N*H* 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 [*C*HCH(CO_2Et)NH], 52.4, 52.7 (2×CO_2CH_3), 61.6 ($CO_2CH_2CH_3$), 63.0 [*C*H(CO_2Et)NH], 66.3 [C(CO_2Me)CH_3], 172.8, 173.5, 176.3 (3×*C*O_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 calcd for $C_{12}H_{19}NO_6$: 273.1212, found: 273.1214.

4.2.11. 2-Ethyl 3,5-dimethyl (2R,3S*,5R*)-5-methylpyrrolidine-2,3,5-tricarboxylate (endo-trans-**2f**).*[14] Yellowish oil; IR (neat) ν_{max} 2983, 2953, 1732, 1725, 1703 cm^{-1}; ^{1}H NMR δ_H: 1.25 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.37 [s, 3H, C(CO_2CH_3)C*H*$_3$], 2.01 [dd, *J*=13.5, 8.0 Hz, 1H, C*H*HC(CO_2Me)CH_3], 2.68 [dd, *J*=13.5, 7.2 Hz, 1H, C*H*HC(CO_2Me)CH_3], 3.30 [ddd, *J*=8.0, 7.2, 7.0 Hz, 1H, C*H*CH(CO_2Et)], 3.62, 3.73 (2s, 3H, CO_2CH_3), 4.03 [d, *J*=7.0 Hz, 1H, C*H*(CO_2Et)NH], 4.15 (q, *J*=7.2 Hz, 2H, $CO_2CH_2CH_3$), N*H* 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 [*C*HCH(CO_2Et)NH], 53.3, 53.4 (2×CO_2CH_3), 61.4 ($CO_2CH_2CH_3$), 62.8 [*C*H(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 calcd for $C_{12}H_{19}NO_6$: 273.1212, found: 273.1215.

4.2.12. 5-Ethyl 2,3-dimethyl (2S,3R*,5R*)-2-methylpyrrolidine-2,3,5-tricarboxylate (endo-cis-**2f**).*[14] Yellowish oil; 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, *C*HC(CO_2Me)CH_3], 3.65, 3.66 (2s, 3H, CO_2CH_3), 3.87 [dd, *J*=8.6, 7.6 Hz, 1H, *C*H(CO_2Et)NH], 4.15 (q, *J*=7.1 Hz, 2H, $CO_2CH_2CH_3$), N*H* nd; ^{13}C NMR δ_C: 14.3 ($CO_2CH_2CH_3$), 25.5 [CHC(CO_2Me)CH_3], 32.3 [*C*H_2CH(CO_2Et)NH], 52.0, 52.1 (2×CO_2CH_3), 52.5 [CHC(CO_2Me)Me], 58.0 [*C*H(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 calcd for $C_{12}H_{19}NO_6$: 273.1212, found: 273.1214.

4.2.13. Diethyl (1S,3R*,3aS*,6aR*)-1-benzyl-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1,3-dicarboxylate (endo-cis-**3a**).*[14] Sticky pale yellow oil; 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, *C*H_2Ph) 2.92 (s, 3H, NCH_3), 3.38 [d, *J*=8.0 Hz, 1H, *C*HC(CO_2Et)Bn], 3.55 [deform. dd, *J*=8.4, 8.0 Hz, 1H, *C*HCH(CO_2Et)NH], 4.09 [d, *J*=8.4 Hz, 1H, *C*H(CO_2Et)NH], 4.24 (q, *J*=7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.26 (q, *J*=7.2 Hz, 2H, $CO_2CH_2CH_3$), N*H* nd; ^{13}C NMR δ_C: 14.0 (2×$CO_2CH_2CH_3$), 25.4 (NCH_3), 42.2 (CH_2Ar), 50.4 [*C*HCH(CO_2Et)NH], 56.6 [*C*HC(CO_2Et)Bn], 62.0 [*C*H(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 (ArC)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 calcd for $C_{20}H_{24}N_2O_6$: 388.1634, found: 388.1631.

4.2.14. Diethyl (1S,3R*,3aS*,6aR*)-1,5-dibenzyl-4,6-dioxoocta hydropyrrolo[3,4-c]pyrrole-1,3-dicarboxylate (endo-cis-**3b**).*[14] Colourless prisms, mp=127–130 °C (from hexane/$CDCl_3$); 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 (2d, *J*=13.9 Hz, 2H, *C*H_2Ph), 3.38 [d, *J*=7.8 Hz, 1H, *C*HC(CO_2Et)Bn], 3.55 [deform. dd, *J*=7.8, 7.8 Hz, 1H, *C*HCH(CO_2Et)NH], 4.03–4.27 [m, 5H, 2×$CO_2CH_2CH_3$ and C*H*(CO_2Et)NH], 4.54, 4.60 (d, *J*=14.3 Hz, 2H), 7.20–7.35 (m, 10H, 2×CH_2*Ph*), 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_2Et)NH], 56.6 [*C*HCH(CO_2Et)NH], 61.9, 62.1 (2×$CO_2CH_2CH_3$), 62.3 [*C*H(CO_2Et)NH], 73.7 [*C*Bn(CO_2Et)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 calcd for $C_{26}H_{28}N_2O_6$–C_7H_7: 373.1400, found: 373.1401.

4.2.15. Diethyl (1S,3R*,3aS*,6aR*)-1-benzyl-4,6-dioxo-5-phenyl octahydropyrrolo[3,4-c]pyrrole-1,3-dicarboxylate (endo-cis-**3c**).*[14] Colourless prisms, mp=169–172 °C (from hexane/$CDCl_3$); 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, *C*H_2Ph), 3.51 (s, 1H, N*H*), 3.55 [d, *J*=7.8 Hz, 1H, *C*HC(CO_2Et)Bn], 3.73 [deform. dd, *J*=7.8, 7.8 Hz, 1H, *C*HCH(CO_2Et)NH], 4.15–4.30 [m, 5H, 2×$CO_2CH_2CH_3$ and C*H*(CO_2Et)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_2Et)NH], 56.6 [*C*HCH(CO_2Et)NH], 62.1, 62.2 (2×$CO_2CH_2CH_3$), 62.3 [*C*H(CO_2Et)NH], 74.1 [*C*Bn(CO_2Et)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 calcd for $C_{25}H_{26}N_2O_6$: 450.1791, found: 450.1801.

4.2.16. 5-Ethyl 2,3,4-trimethyl (2S,3S*,4S*,5R*)-2-benzylpyrrolidine-2,3,4,5-tetracarboxylate (endo-cis-**3d**).*[14] Colourless oil; 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, *C*H_2Ph), 3.34 [d, *J*=10.1 Hz, 1H, *C*HC(CO_2Et)Bn], 3.65 [dd, *J*=10.1, 8.5 Hz, 1H, *C*HCH(CO_2Et)NH], 3.70, 3.78 (2s, 3H, CO_2CH_3), 3.86 [d, *J*=8.5 Hz, 1H, *C*H(CO_2Et)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 [CHC(CO_2Et)Bn], 52.4, 52.6 (2×CO_2CH_3), 54.8 [CHCH(CO_2Et)NH], 61.6 [*C*H(CO_2Et)NH], 62.0, 61.7 (2×$CO_2CH_2CH_3$), 72.3 [*C*(CO_2Et)Bn], 127.1, 128.3, 130.9, 135.9 (ArC), 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 calcd for $C_{20}H_{25}NO_8$: 407.1580, found: 407.1586.

4.2.17. Diethyl (2R,3S*,4S*,5S*)-2-benzyl-3,4-bis(phenylsulfonyl) pyrrolidine-2,5-dicarboxylate (exo-cis-**3e**).*[14] Pale yellow prisms, mp: 85–86 °C (from *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, *C*H_2Ph), 3.88–4.29 (m, 4H, 2×$CO_2CH_2CH_3$), 4.20 [*C*H(CO_2Et)NH], 4.43 (br s, 1H, N*H*), 4.51 [d, *J*=5.2 Hz, 1H, *C*HC(CO_2Et)Bn], 4.89 [deform. dd, *J*=5.2, 5.2 Hz, 1H, *C*HCH(CO_2Et)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_2Et)NH], 69.4 [CHCBn(CO_2Et)NH], 72.0 [*C*H(CO_2Et)NH], 73.8 [*C*Bn(CO_2Et)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 (ArC), 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 calcd for $C_{29}H_{31}NO_8S_2$–$C_3H_5O_2$: 512.1202, found: 512.1215.

4.2.18. 3-Ethyl 1-methyl (1R,3R*,3aS*,6aR*)-5-methyl-4,6-dioxo-1-phenyloctahydropyrrolo[3,4-c]pyrrole-1,3-dicarboxylate (endo-cis-**4a**).*[14] Sticky pale yellow oil; 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*HCHCO_2Et], 3.69 (s, 3H, CO_2CH_3), 3.76 [d, *J*=8.5, 1H, C*H*(CO_2Et)NH], 3.96 [d, *J*=7.5 Hz, 1H, *C*H(CO_2Me)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_2Et)NH], 53.4 [CHC(CO_2Me)Ph], 56.5 (*C*HCO_2Et), 61.6 (CO_2CH_3), 62.1 ($CO_2CH_2CH_3$), 74.8 [*C*(CO_2Me)Ph], 127.4, 128.5, 128.7, 138.1 (ArC), 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 calcd for $C_{18}H_{20}N_2O_6$: 360.1321, found: 360.1322.

4.2.19. 3-Ethyl 1-methyl (1S,3R*,3aS*,6aR*)-5-methyl-4,6-dioxo-1-phenyloctahydropyrrolo[3,4-c]pyrrole-1,3-dicarboxylate (endo-trans-**4a**).*[14] Sticky pale yellow oil; 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*HCHCO_2Et], 3.79 (s, 3H, CO_2CH_3), 3.86 [dd, *J*=7.6, 3.5 Hz, 1H, *C*H(CO_2Et)NH], 4.25 [d, *J*=7.6 Hz, 1H, *C*HC(CO_2Me)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 [CHCH(CO_2Et)NH], 50.4 [*C*HC(CO_2Me)Ph], 53.7 (*C*HCO_2Et), 59.8 (CO_2CH_3), 61.7 ($CO_2CH_2CH_3$), 74.1 [*C*(CO_2Me)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 calcd for $C_{18}H_{20}N_2O_6$: 360.1321, found:360.1336.

4.2.20. 5-Ethyl 2,3,4-trimethyl (2R,3S*,4S*,5R*)-2-phenylpyrrolidine-2,3,4,5-tetracarboxylate (endo-cis-**4d**).*[14] Colourless oil; 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, C*H*CH(CO_2Et)NH], 3.98 [d, *J*=8.5 Hz, 1H, C*H*(CO_2Et)NH], 4.04 (q, *J*=7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.38 [d, *J*=10.1 Hz, 1H, C*H*C(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 [*C*HC(CO_2Me)Ph], 53.5 [*C*HCH(CO_2Et)NH], 60.7 [*C*H(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 calcd for $C_{19}H_{23}NO_8$: 393.1424, found: 393.1421.

4.2.21. 5-Ethyl 2,3,4-trimethyl (2R,3R*,4R*,5R*)-2-phenylpyrrolidine-2,3,4,5-tetracarboxylate (exo-cis-**4d**).*[14] Colourless oil; IR (neat) ν_{max} 2990, 2950, 1748, 1733, 1730, 1715 cm^{-1}; ^1H NMR δ_H: 1.30 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$ CO_2Et)NH], 4.86 [d, *J*=5.3 Hz, 1H, C*H*C(CO_2Me)Ph], 4.91 [deform. dd, *J*=5.3, 5.0 Hz, 1H, C*H*CHCO$_2$Et], 7.35–8.05 (m, 15H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 14.0 ($CO_2CH_2CH_3$), 53.2 [*C*H(CO_2Et)NH], 60.9 (CO_2CH_3), 62.3 ($CO_2CH_2CH_3$), 69.4 [CHCH(CO_2Et)NH], 74.6 [*C*HC(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 calcd for $C_{27}H_{27}NO_8S_2$:557.1168, found: 557.1173.

4.2.22. 5-Ethyl 2,3-dimethyl (2R,3R*,5R*)-2-phenylpyrrolidine-2,3,5-tricarboxylate (endo-cis-**4f**).*[14] Yellowish oil; 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*$_2$CH(CO_2Et)], 3.51 [dd, *J*=7.6, 4.5 Hz, 1H, C*H*C(CO_2Me)Ph], 3.68, 3.70 (2s, 3H, CO_2CH_3), 3.85 [dd, *J*=9.0, 5.7 Hz, 1H, C*H*(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*$_2$CH(CO_2Et)NH], 52.2, 52.9 (2×CO_2CH_3), 54.0 [*C*HC(CO_2Me)Ph], 58.6 [*C*H(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 calcd for $C_{17}H_{21}NO_6$: 335.1369, found:335.1313.

4.2.23. 5-Ethyl 2,3-dimethyl (2S,3R*,5R*)-2-phenylpyrrolidine-2,3,5-tricarboxylate (endo-trans-**4f**).*[14] 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*$_2$CH(CO_2Et)], 3.19, 3.72 (2s, 3H, CO_2CH_3), 3.92 [deform. dd, *J*=8.0, 7.6 Hz, Ph1H, C*H*C(CO_2Me)Ph], 4.04 [deform. dd, *J*=6.5, 5.9 Hz, 1H, C*H*(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*$_2$CH(CO_2Et)NH], 50.6, 51.5 (2×CO_2CH_3), 53.4 [*C*HC(CO_2Me)Ph], 58.5 [*C*H(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 calcd for $C_{17}H_{21}NO_6$: 335.1369, found: 335.1308.

4.2.24. 5-Ethyl 2-methyl (2R,3R*,4R*,5S*)-2-phenyl-3,4-bis(phenylsulfonyl)pyrrolidine-2,5-dicarboxylate (exo-trans-**4e**).*[14] 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, C*H*($OMe)_2$NH], 3.40 [dd, *J*=7.6, 4.8 Hz, 1H, C*H*CH($OMe)_2$NH], 3.42, 3.54 (2s, 6H, 2×OCH_3), 3.51 [deform. dd, *J*=7.9, 7.6 Hz, 1H, C*H*CH(CO_2Et)NH], 3.85 [d, *J*=7.6 Hz, 1H, C*H*(CO_2Et)NH], 4.30 (q, *J*=7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.69 [d, *J*=4.8 Hz, 1H, C*H*($OMe)_2$], ^{13}C NMR δ_C: 14.2 ($CO_2CH_2CH_3$), 25.2 (NCH_3), 45.5 [*C*HCH($OMe)_2$NH], 49.1 [CHCH(CO_2Et)NH], 55.8, 56.0 (2×OCH_3), 61.7 ($CO_2CH_2CH_3$), 62.3 [CH(CH($OMe)_2$)NH], 63.4 [*C*H(CO_2Et)NH], 102.6 [*C*H($OMe)_2$], 169.6 (*C*O$_2$Et), 175.6, 175.9 (2×CON); MS (EI-GC) *m/z*: 300 (M^+, <1%), 269 (13), 225 (27), 195 (34), 179 (10), 151 (18), 94 (16), 75 (100); HRMS calcd for $C_{13}H_{20}N_2O_6$+1: 301.1399, found: 301.1399.

4.2.25. Ethyl (1S,3R*,3aS*,6aR*)-3-(dimethoxymethyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (endo-cis-**5a**).* Yellow prisms, mp: 105–108 °C (from hexane/CH_2Cl_2); IR (neat) ν_{max} 2980, 1719, 1696 cm^{-1}; ^1H NMR δ_H: 1.35 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.50 (br s, 1H, N*H*), 2.95 (s, 3H, NCH_3), 3.27 [deform. dd, *J*=7.9, 7.6 Hz, 1H, C*H*CH(CH(), 3.56, 3.69, 3.72 (3s, 3H, CO_2CH_3)], 3.64 [deform. dd, *J*=6.9, 6.7 Hz, 1H, C*H*CH(CO_2Et)NH], 3.89 [d, *J*=6.7 Hz, 1H, C*H*C(CO_2Me)Ph], 4.17 [d, *J*=6.9 Hz, 1H, C*H*(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 [*C*HC(CO_2Me)Ph], 54.7 [CHCH(CO_2Et)NH], 61.6 [*C*H(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 calcd for $C_{19}H_{23}NO_8$: 393.1424, found: 393.1426.

4.2.26. Ethyl (1S,3R*,3aS*,6aR*)-5-benzyl-3-(dimethoxymethyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (endo-cis-**5b**).* Sticky pale yellow oil; IR (neat) ν_{max} 2968, 2308, 1716, 1695 cm^{-1}; ^1H NMR δ_H: 1.32 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.50 (br s, 1H, N*H*), 3.16, 3.47 (2s, 6H, 2×OCH_3), 3.25 [deform. dd, *J*=8.0, 7.7 Hz, 1H, C*H*CH(CH($OMe)_2$)NH], 3.40 [dd, *J*=8.0, 4.0 Hz, 1H, C*H*CH(O-Me)$_2$NH], 3.51 [deform. dd, *J*=7.7, 7.6 Hz, 1H, C*H*CH(CO_2Et)NH], 3.87 [d, *J*=7.6 Hz, 1H, C*H*(CO_2Et)NH], 4.29 (q, *J*=7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.54 (d, *J*=14.3 Hz, 1H, NC*H*HPh), 4.65 [d, *J*=4.0 Hz, 1H, C*H*($OMe)_2$], 4.68 (d, *J*=14.3 Hz, 1H, NC*H*HPh) 7.23–7.34 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 14.2 ($CO_2CH_2CH_3$), 42.7 (NCH_2Ph), 46.8 [CHCH(CH($OMe)_2$)NH], 49.4 [CHCH(CO_2Et)NH], 55.4, 55.7 (2×OCH_3), 61.6 ($CO_2CH_2CH_3$), 62.7 [CH(CH($OMe)_2$)NH], 63.7 [*C*H(CO_2Et)NH], 102.0 [CH($OMe)_2$], 127.9, 128.5, 128.6, 135.6 (Ar*C*), 169.4 (*C*O$_2$Et), 175.3, 175.5 (2×CON); MS (EI-GC) *m/z*: 376 (M^+, <1%), 301 (29), 271 (15), 243 (10), 227 (18), 94 (10), 75 (100); HRMS calcd for $C_{19}H_{24}N_2O_6$+1: 377.1712, found: 377.1701.

4.2.27. Ethyl (1S,3R*,3aS*,6aR*)-3-(dimethoxymethyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (endo-cis-**5c**).* Yellowish prisms, mp: 98–102 °C (from hexane/CH_2Cl_2); IR (neat) ν_{max} 2995, 2939, 2310, 1718, 1700 cm^{-1}; ^1H NMR δ_H: 1.32 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.55 (br s, 1H, N*H*), 3.39 (s, 3H, OCH_3), 3.43 [deform. dd, *J*=7.7, 7.2 Hz, 1H, C*H*CH(CH($OMe)_2$)NH], 3.50–3.55 (m, 4H, C*H*CH($OMe)_2$NH, OCH_3), 3.66 [deform. dd, *J*=7.7, 7.2 Hz, 1H, C*H*CH(CO_2Et)NH], 3.97 [d, *J*=7.7 Hz, 1H, C*H*(CO_2Et)NH], 4.28 (q, *J*=7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.79 [d, *J*=4.0 Hz, 1H, C*H*($OMe)_2$], 7.24–7.51 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 14.2 ($CO_2CH_2CH_3$), 47.1 [CHCH(CH($OMe)_2$)NH], 49.5 [CHCH(CO_2Et)NH], 55.8, 55.9 (2×OCH_3), 61.8 ($CO_2CH_2CH_3$), 62.9 [CH(CH($OMe)_2$)NH], 64.1 [CH(CO_2Et)NH], 102.2 [CH($OMe)_2$], 126.7, 128.9, 129.3, 131.9 (Ar*C*), 169.6 (*C*O$_2$Et), 174.8, 175.0 (2×CON); MS (EI-GC) *m/z*: 362 (M^+,

<1%), 331 (11), 287 (29), 257 (24), 94 (21), 75 (100); HRMS calcd for $C_{18}H_{22}N_2O_6$+1: 363.1556, found: 363.1550.

4.2.28. Methyl (1S,3R*,3aS*,6aR*)-3-(dimethoxymethyl)-1,5-dimethyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (endo-cis-**6a**).* Yellow solid, mp: 120–123 °C (from hexane/CH_2Cl_2); IR (neat) ν_{max} 2976, 1720, 1702 cm^{-1}; ^1H NMR δ_H: 1.47 [s, 3H, C(CO_2CH_3)CH_3], 2.92 (s, 3H, NCH_3), 3.20 [d, *J*=7.7 Hz, 1H, C*H*C(CO_2Me)CH_3], 3.34 [deform. dd, *J*=8.6, 7.7 Hz, 1H, C*H*CH(CH(OMe)$_2$)NH], 3.38 3.51 (2s, 6H, 2×OCH_3), 3.68 (dd, *J*=8.6, 3.0 Hz, 1H, C*H*CH(OMe)$_2$NH), 3.83 (s, 3H, CO_2CH_3), 4.76 [d, *J*=3.0 Hz, 1H, C*H*(OMe)$_2$], N*H* nd; ^{13}C NMR δ_C: 24.1 [C(CO_2CH_3)CH_3], 25.1 (NCH_3), 47.6 [CHCH(CH(OMe)$_2$)NH], 52.9 [CHC(CO_2Me)CH_3], 55.7, 56.0 (2×OCH_3), 56.7 (CO_2CH_3), 62.4 [CH(CH(OMe)$_2$)NH], 68.3 [C(CO_2Me)CH_3], 101.9 [CH(OMe)$_2$], 172.3 (CO_2Me), 175.7, 176.1 (2×CON); MS (EI-GC) *m/z*: 300 (M^+, <1%), 241 (13), 225 (37), 209 (24), 165 (40), 108 (20), 75 (100); HRMS calcd for $C_{13}H_{20}N_2O_6$+1: 301.1399, found: 301.1392.

4.2.29. Trimethyl (2S,3S*,4S*,5R*)-5-(dimethoxymethyl)-2-methylpyrrolidine-2,3,4-tricarboxylate (endo-cis-**6d**).* Sticky pale yellow oil; IR (neat) ν_{max} 2987, 1715, 1713, 1692 cm^{-1}; ^1H NMR δ_H: 1.60 [s, 3H, C(CO_2CH_3)CH_3], 3.25 [deform. dd, *J*=10.5, 8.3 Hz, 1H, C*H*CH(CH(OMe)$_2$)NH], 3.34 [d, *J*=10.5 Hz, 1H, C*H*C(CO_2Me)CH_3], 3.40 (s, 6H, 2×OCH_3), 3.60 (dd, *J*=8.3, 6.2 Hz, 1H, C*H*CH(OMe)$_2$NH), 3.68 (s, 6H, 2×CO_2CH_3), 3.74 (s, 3H, CO_2CH_3), 4.33 [d, *J*=6.2 Hz, 1H, C*H*(OMe)$_2$], N*H* nd; ^{13}C NMR δ_C: 25.6 [C(CO_2CH_3)CH_3], 49.2 [CHCH(CH(OMe)$_2$)NH], 52.2 [CHC(CO_2Me)CH_3], 52.3, 52.4 (2×OCH_3), 54.5, 55.5, 58.0 (3×CO_2CH_3), 62.3 [CH(CH(OMe)$_2$)NH], 67.9 [C(CO_2Me)CH_3], 106.1 [CH(OMe)$_2$], 171.0, 173.4, 174.4 (3×CO_2Me); MS (EI-GC) *m/z*: 333 (M^+, <1%), 258 (11), 215 (15), 200 (12), 156 (31), 75 (100); HRMS calcd for $C_{14}H_{23}NO_8$+1: 334.1502, found: 334.1525.

4.2.30. Ethyl (1S,3R*,3aS*,6aR*)-1-benzyl-3-(dimethoxymethyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (endo-cis-**7a**).* Yellowish prisms, mp: 85–88 °C (from hexane/CH_2Cl_2); IR (neat) ν_{max} 2988, 2335, 1717, 1699 cm^{-1}; ^1H NMR δ_H: 1.34 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.79 (br s, 1H, N*H*), 2.92 (d, *J*=13.7 Hz, 1H, C*H*HPh), 2.93 (s, 3H, NCH_3), 3.30–3.35 [m, 6H, C*H*HPh, C*H*CH(CH(OMe)$_2$)NH, C*H*C(CO_2Et)BnNH, OCH_3], 3.49 (s, 3H, OCH_3), 3.66 [m, 1H, C*H*CH(OMe)$_2$NH], 4.26 (q, *J*=7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.68 [d, *J*=4.1 Hz, 1H, C*H*(OMe)$_2$], 7.19–7.30 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 14.2 ($CO_2CH_2CH_3$), 24.2 (NCH_3), 41.0 [CHC(CO_2Et)BnNH], 47.1 [CHCH(CH(OMe)$_2$)NH], 55.0 (CH_2Ph), 55.7, 55.8 (2×OCH_3), 61.5 ($CO_2CH_2CH_3$), 61.9 [CH(CH(OMe)$_2$)NH], 74.2 [C(CO_2Et)BnNH], 102.1 [CH(OMe)$_2$], 127.3, 128.5, 130.2, 135.8 (ArC), 170.7 (CO_2Et), 175.5, 175.9 (2×CON); MS (EI-GC) *m/z*: 390 (M^+, <1%), 315 (26), 299 (27), 285 (13), 269 (14), 268 (14), 267 (100), 91 (13), 75 (13); HRMS calcd for $C_{20}H_{26}N_2O_6$+1: 391.1869, found: 391.1875.

4.2.31. Ethyl (1S,3R*,3aS*,6aR*)-1,5-dibenzyl-3-(dimethoxymethyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (endo-cis-**7b**).* Yellowish prisms, mp: 92–94 °C (from hexane/CH_2Cl_2); IR (neat) ν_{max} 2996, 2938, 2310, 1715, 1700 cm^{-1}; ^1H NMR δ_H: 1.29 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.86 (br s, 1H, N*H*), 2.92 (d, *J*=13.8 Hz, 1H, C*H*HPh), 3.08, 3.41 (2s, 6H, 2×OCH_3), 3.28–3.35 [m, 3H, C*H*HPh, C*H*CH(CH(OMe)$_2$)NH, C*H*C(CO_2Et)BnNH], 3.63 [dd, *J*=7.4, 3.8 Hz, 1H, C*H*CH(OMe)$_2$NH], 4.23 (q, *J*=7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.54, 4.66 (d, *J*=14.4 Hz, 2H, NCH_2Ph), 4.61 [d, *J*=3.8 Hz, 1H, C*H*(OMe)$_2$], 7.20–7.33 (m, 10H, Ar*H*); ^{13}C NMR δ_C: 14.1 ($CO_2CH_2CH_3$), 41.1, 42.7 (CH_2Ph, NCH_2Ph), 47.1 [CHC(CO_2Et)BnNH], 54.5 [CHCH(CH(OMe)$_2$)NH], 55.4, 55.6 (2×OCH_3), 61.8 [CH(CH(OMe)$_2$)NH], 62.0 ($CO_2CH_2CH_3$), 72.5 [C(CO_2Et)BnNH], 101.7 [CH(OMe)$_2$], 127.2, 127.9, 128.4, 128.5, 128.6, 130.2, 135.6, 135.9 (ArC), 170.6 (CO_2Et), 175.2, 175.5 (2×CON); MS (EI-GC) *m/z*: 466 (M^+, <1%), 308 (12), 307 (55), 290 (16), 289 (100), 281 (11), 215 (14), 207 (21), 187 (12), 174 (15), 119 (11), 91 (64); HRMS calcd for $C_{26}H_{30}N_2O_6$+1: 467.2182, found: 467.2175.

4.2.32. Ethyl (1S,3R*,3aS*,6aR*)-1-benzyl-3-(dimethoxymethyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (endo-cis-**7c**).* Yellowish solid, mp: 118–121 °C (from hexane/CH_2Cl_2); IR (neat) ν_{max} 2992, 2945, 2315, 1718, 1689 cm^{-1}; ^1H NMR δ_H: 1.33 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 3.01, 3.39 (2d, *J*=13.7 Hz, 2H, CH_2Ph), 3.34, (s, 3H, OCH_3), 3.47–3.53 [m, 5H, C*H*CH(CH(OMe)$_2$)NH, C*H*C(CO_2Et)BnNH, OCH_3], 3.74 [dd, *J*=7.8, 3.4 Hz, 1H, C*H*CH(OMe)$_2$NH], 4.26 (qd, *J*=7.2, 2.1 Hz, 2H, $CO_2CH_2CH_3$), 4.82 [d, *J*=3.8 Hz, 1H, C*H*(OMe)$_2$], 7.23–7.50 (m, 10H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 14.0 ($CO_2CH_2CH_3$), 41.3 (CH_2Ph), 47.5 [CHC(CO_2Et)BnNH], 54.7 [CHCH(CH(OMe)$_2$)NH], 55.6, 56.0 (2×OCH_3), 62.0 [CH(CH(OMe)$_2$)NH], 62.2 ($CO_2CH_2CH_3$), 72.8 [C(CO_2Et)BnNH], 101.6 [CH(OMe)$_2$], 126.6, 127.2, 128.3, 128.8, 129.2, 130.2, 131.8, 135.8 (ArC), 170.6 (CO_2Et), 174.6, 174.9 (2×CON); MS (EI-GC) *m/z*: 452 (M^+, <1%), 315 (23), 299 (24), 285 (13), 269 (15), 268 (15), 267 (100), 241 (10), 91 (29), 75 (35); HRMS calcd for $C_{25}H_{28}N_2O_6$+1: 453.2025, found: 453.2014.

4.2.33. 2-Ethyl 3,4-dimethyl (2S,3R*,4R*,5R*)-2-benzyl-5-(dimethoxymethyl)pyrrolidine-2,3,4-tricarboxylate (exo-cis-**7d**).* Sticky pale yellow oil; IR (neat) ν_{max} 2985, 2947, 1714, 1712, 1691 cm^{-1}; ^1H NMR δ_H: 1.26 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.76, 2.95 (d, *J*=13.0 Hz, 2H, CH_2Ph), 3.29, 3.34 (s, 6H, 2×OCH_3), 3.68–3.73 [m, 6H, C*H*CH(CH(OMe)$_2$)NH, C*H*C(CO_2Et)BnNH, C*H*CH(OMe)$_2$NH, CO_2CH_3], 3.79 (s, 3H, CO_2CH_3), 4.07–4.23 [m, 3H, C*H*(OMe)$_2$, $CO_2CH_2CH_3$], 7.16–7.22 (m, 5H, Ar*H*), N*H* nd; ^{13}C NMR δ_C: 14.2 ($CO_2CH_2CH_3$), 42.0 (CH_2Ph), 47.9 [CHC(CO_2Et)BnNH], 52.0 [CHCH(CH(OMe)$_2$)NH], 52.4, 53.1 (2×$COCH_3$), 54.5, 54.8 (2×OCH_3), 59.7 [CH(CH(OMe)$_2$)NH], 61.7 ($CO_2CH_2CH_3$), 69.9 [C(CO_2Et)BnNH], 103.8 [CH(OMe)$_2$], 126.8, 128.0, 130.6, 136.3 (ArC), 171.3, 171.6 (2×CO_2Me), 174.1 (CO_2Et); MS (EI-GC) *m/z*: 423 (M^+, <1%), 392 (14), 350 (19), 348 (45), 332 (36), 318 (21), 317 (13), 316 (68), 301 (11), 300 (76), 288 (39), 286 (11), 268 (59), 258 (26), 256 (15), 242 (16), 240 (15), 226 (20), 224 (11), 216 (11), 210 (18), 196 (13), 194 (17), 166 (11), 91 (100), 75 (28); HRMS calcd for $C_{21}H_{29}NO_8$+1: 424.1971, found: 424.1968.

4.2.34. 2-Ethyl 3,4-dimethyl (2S,3S*,4S*,5R*)-2-benzyl-5-(dimethoxymethyl)pyrrolidine-2,3,4-tricarboxylate (endo-cis-**7d**).* Sticky pale yellow oil; IR (neat) ν_{max} 2987, 2955, 1719, 1716, 1696 cm^{-1}; ^1H NMR δ_H: 1.24 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.61 (br s, 1H, N*H*), 3.12–1.19 [m, 2H, C*H*HPh, C*H*CH(CH(OMe)$_2$)NH], 3.29–3.40 [m, 9H, C*H*HPh, C*H*C(CO_2Et)BnNH, C*H*CH(OMe)$_2$NH, 2×OCH_3], 3.69 (s, 3H, CO_2CH_3), 3.77 (s, 3H, CO_2CH_3), 4.05–4.15 [m, 2H, $CO_2CH_2CH_3$], 4.36 [d, *J*=6.4 Hz, 1H, C*H*(OMe)$_2$], 7.17–7.27 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 14.1 ($CO_2CH_2CH_3$), 43.1 (CH_2Ph), 49.0 [CHC(CO_2Et)BnNH], 52.2, 52.3 (2×$COCH_3$), 53.8 [CHCH(CH(OMe)$_2$)NH], 55.2, 55.7 (2×OCH_3), 61.7 [CH(CH(OMe)$_2$)NH], 61.9 ($CO_2CH_2CH_3$), 72.0 [C(CO_2Et)BnNH], 105.9 [CH(OMe)$_2$], 127.1, 128.3, 130.7, 136.1 (ArC), 171.1, 173.1 (2×CO_2Me), 173.4 (CO_2Et); MS (EI-GC) *m/z*: 423 (M^+, <1%), 348 (11), 333 (11), 332 (65), 316 (33), 300 (45), 288 (46), 286 (11), 268 (61), 258 (33), 256 (14), 242 (14), 240 (17), 226 (21), 216 (12), 210 (17), 194 (16), 166 (10), 91 (100), 75 (27); HRMS calcd for $C_{21}H_{29}NO_8$+1: 424.1971, found: 424.1959.

4.2.35. Diethyl (3R,3aS*,6aR*)-3-(dimethoxymethyl)-5-methyl-4,6-dioxohexahydropyrrolo[3,4-c]pyrrole-1,1(2H)-dicarboxylate (all-cis-**8**).* Sticky pale yellow oil; IR (neat) ν_{max} 2999, 1718, 1713, 1691 cm^{-1}; ^1H NMR δ_H: 1.29 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.33 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.97 (s, 3H, NCH_3), 3.32 (deform. dd, *J*=7.8, 7.5 Hz, 1H, C*H*CHNH), 3.42, 3.54 (2s, 6H, 2×OCH_3), 4.08 [d, *J*=7.5 Hz, 1H, C*H*C(CO_2Et)$_2$NH], 4.18–4.40 (m, 5H, C*H*NH, 2×$CO_2CH_2CH_3$), 4.56 [d, *J*=6.1 Hz, 1H, C*H*(OMe)$_2$], N*H* nd; ^{13}C NMR

δ_C: 14.1, 14.2 (2×$CO_2CH_2CH_3$), 25.4 (NCH_3), 45.5 (*C*HCHNH), 50.6 [*C*HC(CO_2Et)$_2$NH], 55.5, 56.2 (2×OCH_3), 60.9 (*C*HNH), 62.6, 62.9 (2×$CO_2CH_2CH_3$), 74.1 [*C*(CO_2Et)$_2$], 103.5 [*C*H(OMe)$_2$], 166.9, 169.3 (2×*C*O_2Et), 175.2, 175.4 (2×CON); MS (EI-GC) *m/z*: 372 (M^+, <1%), 341 (14), 299 (24), 298 (10), 297 (52), 268 (10), 267 (65), 166 (30), 75 (100); HRMS calcd for $C_{16}H_{24}N_2O_8$+1: 373.1611, found: 373.1599.

4.2.36. Methyl (1S,3R*,3aS*,6aR*)-3-benzoyl-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (endo-cis-**9a**).* Pale yellow oil; IR (neat) ν_{max}: 2359, 1749, 1693, 1676, 1435, 1286, 1209, 1129, 701 cm^{-1}; ^{1}H-RMN δ_H: 2.92 (s, 3H, NMe), 3.01 (br s, 1H, NH), 3.10–2.95, 3.80–3.74 (2m, 2H, 2×CHCON), 3.83 (s, 3H, OMe), 4.46 (d, *J*=1.0 Hz, 1H, 2×CHCON), 5.11 (d, *J*=7.6 Hz, 1H, C*H*COPh), 7.55–7.49 (m, 2H, Ar*H*), 7.67–7.60 (m, 1H, Ar*H*), 8.02–7.97 (m, 2H, Ar*H*); ^{13}C-RMN δ_C: 25.6 (CH_3N), 50.1 (CH_3O), 50.7, 53.1 (2×*C*CHON), 62.7, 64.6 (2×CHN), 128.3, 129.0, 134.1, 136.1 (Ar*C*), 172.4, 175.1, 176.6, 195.8 (4×CO); MS (EI) *m/z* (%): 316 (M^+, 1%), 211 (100), 151 (18), 105 (20), 94 (25), 77 (13); HRMS calcd for ($C_{16}H_{16}N_2O_5$): 316.1059, found: 316.1049.

4.2.37. Methyl (1S,3R*,3aR*,6aS*)-3-benzoyl-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (exo-cis-**9a**).* Pale yellow oil; IR (neat) ν_{max}: 2356, 1701, 1441, 1382, 1265, 1125, 732, 699 cm^{-1}; ^{1}H-RMN δ_H 2.59 (br s, 1H, NH), 3.03 (s, 3H, MeN), 3.56 (t, *J*=8.0 Hz, 1H, CHCON), 3.73 (dd, *J*=8.0, 1.5 Hz, 1H, CHCON), 3.82 (s, 3H, OMe), 4.21 (d, *J*=8.1 Hz, 1H, $CHCO_2$), 5.18 (d, *J*=1.6 Hz, 1H, C*H*COPh), 7.56–7.50 (m, 2H, Ar*H*), 7.66–7.61 (m, 1H, Ar*H*), 8.19–8.15 (m, 2H, Ar*H*); ^{13}C-RMN δ_C: 25.7 (MeN), 48.2, 49.7 (2×CHCON), 52.7 (MeO), 61.8, 65.0 (2×CHN), 129.1, 129.4, 133.4, 134.3 (Ar*C*), 170.4, 175.6, 177.5, 196.7 (4×CO); MS (EI) *m/z* (%): 316 (M^+ 1%), 211 (100), 179 (26), 151 (40), 105 (13), 94 (36), 77 (12); HRMS calcd for ($C_{16}H_{16}N_2O_5$): 316.1059, found: 316.1057.

4.2.38. Methyl (1S,3R*,3aS*,6aR*)-3-benzoyl-5-benzyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (endo-cis-**9b**).* Pale yellow oil; IR (neat) ν_{max}: 1735, 1699, 1677, 1438, 1403, 1349, 1288, 1170, 701 cm^{-1}; ^{1}H-RMN δ_H: 2.86 (br s, 1H, NH), 3.69 (dd, *J*=8.3, 8.1 Hz, 1H, CHCON), 3.80 (s, 3H, OMe), 3.83 (dd, *J*=8.3, 8.1 Hz, 1H, CHCON), 4.25 (d, *J*=8.3 Hz, 1H, $CHCO_2$), 4.51, 4.58 (2d, *J*=14.0 Hz, 2H CH_2Ph), 5.09 (d, *J*=8.3 Hz, 1H, C*H*COPh), 7.29–7.27 (m, 5H, Ar*H*), 7.33–7.30 (m, 1H, Ar*H*), 7.52 (t, *J*=7.6 Hz, 2H, Ar*H*), 7.66–7.60 (m, 1H, Ar*H*), 8.03–7.98 (m, 2H, Ar*H*); ^{13}C-RMN δ_C: 43.2 (*C*H_2Ph), 49.8, 50.5 (2×*C*HCON), 51.1 (MeO), 62.7, 64.8 (2×CHN), 128.2, 128.4, 128.8, 128.8, 129.2, 134.3, 135.2, 135.7 (Ar*C*), 169.0, 175.8, 176.0, 195.0 (4×CO); MS (EI) *m/z* (%): 392 (M^+, 1%), 288 (17), 287 (100), 227 (44), 105 (16), 94 (21), 91 (42), 77 (12); HRMS calcd for ($C_{22}H_{20}N_2O_5$): 392.1372, found: 392.1374.

4.2.39. Methyl (1S,3R*,3aS*,6aR*)-3-benzoyl-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (endo-cis-**9c**).* Sticky oil; IR (neat) ν_{max}: 1707, 1669, 1389, 1326, 1290, 1192, 1174, 697 cm^{-1}; ^{1}H-RMN δ_H: 3.68 (br s, 1H, NH), 3.81 (dd, *J*=8.0, 7.9 Hz, 1H, CHCON), 3.86 (s, 3H, OMe), 3.92 (t, *J*=8.0 Hz, 1H, CHCON), 4.31 (d, *J*=8.0 Hz, 1H, $CHCO_2$), 5.15 (d, *J*=7.9 Hz, 1H, C*H*COPh), 7.19–7.13 (m, 2H, Ar*H*), 7.45–7.31 (m, 4H, Ar*H*), 7.50 (t, *J*=7.5 Hz, 2H, Ar*H*), 7.65–7.58 (m, 1H, Ar*H*), 8.03–7.97 (m, 2H, Ar*H*); ^{13}C-RMN δ_C: 50.6 (*C*HCON), 51.1 (MeO), 52.8 (*C*HCON), 63.0, 65.0 (2×CHN), 126.4, 128.2, 128.9, 129.2, 131.1, 134.1, 135.6, 169.4 (Ar*C*), 173.5, 174.0, 174.5, 194.8 (4×CO); MS (EI) *m/z* (%): 378 (M^+, 1%), 273 (100), 241 (15), 213 (15), 126 (13), 110 (25), 94 (75), 77 (25); HRMS calcd for ($C_{21}H_{18}N_2O_5$): 378.1216, found: 378.1209.

4.2.40. Methyl (1S,3R*,3aS*,6aR*)-3-benzoyl-1,5-dimethyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (endo-cis-**10a**).* Pale yellow oil; IR (neat) ν_{max}: 1752, 1698, 1681, 1436, 1281, 1142, 786, 699 cm^{-1}; 1H-RMN δ_H: 1.63 (s, 3H, *Me*C), 2.40 (br s, 1H, NH), 2.87 (s, 3H, MeN), 3.36 (d, *J*=7.7 Hz, 1H, CHCON), 3.91–3.81 (m with s at 3.80, MeO and CHCON), 5.16 (d, *J*=8.3 Hz, 1H, CHN), 7.53 (t, *J*=7.5 Hz, 2H, Ar*H*), 7.68–7.61 (m, 1H, Ar*H*), 8.05–8.00 (m, 2H, Ar*H*); ^{13}C-RMN δ_C: 25.0 (*Me*C), 25.4 (MeN), 51.7 (OMe), 53.2, 57.9 (2×*C*HCON), 63.6, 69.2 (CHNC), 128.4, 129.1, 134.1, 136.1 (Ar*C*), 171.6; 174.5; 175.0; 195.2 (4×CO); MS (EI) *m/z* (%): 330 (M+, 1%), 269 (17%), 225 (100%), 165 (87), 108 (38), 105 (57), 80 (22), 77 (44); HRMS calcd for ($C_{17}H_{18}N_2O_5$-2): 328.1216, found: 328.1215.

4.2.41. Ethyl (1S,3R*,3aS*,6aR*)-3-benzoyl-1-benzyl-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (endo-cis-**11a**).* Pale yellow oil; IR (neat) ν_{max}: 1700, 1684, 1434, 1268, 1129, 1002, 699 cm^{-1}; ^{1}H-RMN δ_H: 1.37 (t, *J*=7.2 Hz, 3H, CH_3CH$_2$), 2.80 (br s, 1H, NH), 2.88 (s, 3H, MeC), 3.18, 3.41 (2×d, *J*=13.9 Hz, 2H, CH_2Ph), 3.57 (d, *J*=7.7 Hz, 1H, CHCON), 3.66 (dd, *J*=8.4, 7.7 Hz, 1H, CHCON), 4.30 (qd, *J*=7.2, 2.0 Hz, 2H, CH_2Me), 4.87 (d, *J*=8.4 Hz, 1H, CHN), 7.39–7.29 (m, 5H, *ArH*), 7.58–7.50 (m, 2H, Ar*H*), 7.69–7.62 (m, 1H, Ar*H*), 7.91 (dd, *J*=5.3, 3.3, 2H, Ar*H*); ^{13}C-RMN δ_C: 14.0 (*Me*C), 25.2 (MeN), 42.9 (*C*H_2Ph), 51.9 (*C*HCON), 57.1 (*C*HCON), 62.4 (CH_2O), 63.2, 73.3 (CHNC), 127.2, 128.1, 128.2, 128.9, 130.5, 133.9, 135.9, 136.0 (Ar*C*), 170.1, 174.4, 174.8, 195.2 (4×CO); MS (EI) *m/z* (%): 420 (M^+, 1%), 347 (30), 330 (35), 315 (100), 269 (36), 241 (30), 184 (20), 156 (25), 105 (46), 91 (43), 77 (32); HRMS calcd for ($C_{24}H_{24}N_2O_5$-2): 418.1685, found: 418.1692.

4.2.42. Ethyl (1S,3R*,3aS*,6aR*)-3-benzoyl-1-benzyl-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (endo-cis-**11b**).* Pale yellow oil; IR (neat) ν_{max}: 1712, 1683, 1497, 1384, 1231, 1002, 699 cm^{-1}; ^{1}H-RMN δ_H: 1.31 (t, *J*=7.2 Hz, 3H, CH_3CH$_2$), 2.40 (br s, 1H, NH), 3.21, 3.42 (2×d, *J*=13.8 Hz, 2H, CH_2Ph), 3.08–3.68 (m, 2H, 2×CHCON), 4.27 (dq, *J*=7.2, 3.7 Hz, 2H, CH$_3$CH_2), 4.92 (d, *J*=8.1 Hz, 1H, CHN), 7.16–7.11 (m, 2H, Ar*H*), 7.43–7.28 (m, 8H, Ar*H*), 7.53–7.45 (m, 2H, Ar*H*), 7.64–7.57 (m, 1H, Ar*H*), 7.88 (dd, *J*=5.2, 3.3 Hz, 2H, Ar*H*); ^{13}C-RMN δ_C: 13.9 (*Me*C), 43.1 (*C*H_2Ph), 51.9, 57.2 (2×CHCON), 62.5 (CH_2O), 63.7, 73.9 (CHNC), 126.5, 127.2, 128.2, 128.3, 128.8, 128.9, 129.1, 130.6, 131.2, 133.9, 135.9, 136.0 (Ar*C*), 170.3, 173.6, 174.0, 195.0 (4×CO); MS (EI) *m/z* (%): 482 (M^+ 1%), 409 (10), 392 (14), 391 (57), 378 (23), 377 (100), 331 (23), 303 (28), 184 (25), 156 (18), 105 (83), 91 (41), 77 (23); HRMS calcd for ($C_{29}H_{26}N_2O_5$-1): 481.1842, found: 481.1832.

4.2.43. 2-Ethyl 3,4-dimethyl (1S,3R*,3aS*,6aR*)-5-benzoyl-2-benzylpyrrolidine-2,3,4-tricarboxylate (endo-cis-**11c**).* Pale sticky oil; IR (neat) ν_{max}: 1733, 1436, 1265, 1203, 732, 700 cm^{-1}; ^{1}H-RMN for major *endo* isomer, δ_H: 1.31–1.17 (m, 3H, CH_3CH$_2$), 2.10 (br s, 1H, NH), 3.22, 3.35 (2×d, *J*=13.5 Hz, 2H, CH_2Ph), 3.43 (s, 3H, MeO), 3.62–3.58 (m, 1H, $CHCO_2$), 3.77 (s, 3H, MeO), 3.81 (d, *J*=4.8 Hz, 1H, $CHCO_2$), 4.19–4.03 (m, 2H, CH_2O), 4.68 (d, *J*=8.8 Hz, 1H, CHN), 7.23–7.14 (m, 2H, Ar*H*), 7.33–7.24 (m, 5H, Ar*H*), 7.40–7.35 (m, 2H, Ar*H*), 7.50–7.43 (m, 4H, Ar*H*), 7.61–7.53 (m, 2H, Ar*H*), 7.88–7.82 (m, 2H, Ar*H*); ^{13}C-RMN for major *endo* isomer δ_C: 14.0 (*Me*C), 42.9 (*C*H_2Ph), 49.7, 52.3, 52.4, 55.3 (2×MeO and 2×*C*HCO_2Me), 62.2 (CH_2O), 64.1, 72.5 (CHNC), 127.2, 128.2, 128.7, 128.8, 130.9, 133.8, 135.5, 135.9 (Ar*C*), 170.6, 172.3, 172.4, 196.8 (4×CO); MS (EI) *m/z* (%): 453 (M^+, 6%), 360 (15), 346 (21), 300 (20), 286 (22), 105 (100), 91 (96), 77 (46); HRMS calcd for ($C_{25}H_{27}NO_7$-2): 451.1788, found: 451.1788.

4.2.44. Diethyl (3R,3aS*,6aR*)-3-benzoyl-5-methyl-4,6-dioxohexahydropyrrolo[3,4-c]pyrrole-1,1(2H)-dicarboxylate (all-cis-**12a**).* Colourless oil; IR (neat) ν_{max}: 1748, 1700, 1685, 1275, 1212, 1173, 1109, 998, 772, 700 cm^{-1}; ^{1}H-RMN δ_H: 1.42–1.29 (m, 6H, 2×CH_3C); 2.00 (br s, 1H, NH), 2.90 (s, 3H, MeN), 3.88 (d, *J*=8.1 Hz, 1H, CHCON), 4.23 (dd, *J*=8.5, 8.1 Hz, 1H, CHCON), 4.52–4.30 (m, 4H, 2×CH_2), 4.87 (d, *J*=8.5 Hz, 1H, CHN), 7.54 (t, *J*=7.5 Hz, 2H, Ar*H*), 7.69–7.61 (m, 1H, Ar*H*), 8.02–7.96 (m, 2H, Ar*H*); ^{13}C-RMN δ_C: 14.1,

14.2 (2×CH_3C), 25.5 (MeN), 51.3, 53.1 (2×CHCON), 63.1, 63.2 (2×CH_2), 63.4, 75.6 (CHNC), 128.3, 129.1, 134.2, 135.9 (ArC), 166.5, 169.1, 174.4, 174.6, 194.6 (5×CO); MS (EI) *m*/*z* (%): 402 (M+, 1%), 329 (12), 297 (100), 223 (10), 166 (62), 138 (10), 105 (46), 77 (23); HRMS calcd for ($C_{20}H_{22}N_2O_7$–CO_2Et): 329.1137, found: 329.1127.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.09.039.

References and notes

1. For recent reviews, see: (a) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; (b) Guillena, G.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693–700; (c) Choudhury, L. H.; Parvin, T. *Tetrahedron* **2011**, *67*, 8213–8228; (d) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237–294; (e) Van Berkel, S. S.; Bögels, B. G. M.; Wijdeven, M. A.; Westermann, B.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2012**, 3543–3559; (f) van der Heijden, G.; Ruijter, E.; Orru, R. V. A. *Synlett* **2013**, 666–685; (g) Brauch, S.; van Berkel, S. S.; Westermann, B. *Chem. Soc. Rev.* **2013**, *42*, 4948–4962; (h) *Multicomponent Reactions in Organic Synthesis*; Zhu, J., Wang.,, Wang, M.-X., Eds.; Wiley-VCH: Weinheim, 2014.
2. For a very recent review, see: Trost, B. M. *Handbook of Green Chemistry*, 2012, Vol. 7, pp 1–33.
3. *Catalysis from A to Z: A Concise Encyclopedia*; Cornils, B., Herrmann, W. A., Muhler, M., Wong, C.-H., Eds.; Wiley-VCH: Weinheim, 2013.
4. (a) *Methods and Applications of Cycloaddition Reactions in Organic Syntheses*; Nishiwaki, N., Ed.; John Wiley & Sons: Hoboken, New Jersey, 2014; (b) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002.
5. For general reviews dealing with general 1,3-DC, see: (a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New Jersey, 2003; (b) Nájera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105–1150; (c) Eberbach, W. *Sci. Synth.* **2004**, *27*, ; Chapter 11441–498; (d) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765–2810; (e) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247–12275; (f) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341–5378.
6. This can be exemplified by the numerous asymmetric 1,3-DC reported. For recent reviews, see: (a) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235–3285; (b) Nájera, C.; Sansano, J. M. In *Topics in Heterocyclic Chemistry*; Hassner, A., Ed.; Springer: Berlin-Heidelberg, 2008; Vol. 12, pp 117–145; (c) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887–2902; (d) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev.* **2008**, *108*, 3174–3198; (e) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132–3148; (f) Nájera, C.; Sansano, J. M.; Yus, M. *J. Braz. Chem. Soc.* **2010**, *21*, 377–412; (g) Kissane, M.; Maguire, A. R. *Chem. Soc. Rev.* **2010**, *39*, 845–883; (h) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, 6784–6794; (i) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2014**, 12434–12446; (j) Nájera, C.; Sansano, J. M. *J. Organomet. Chem.* **2014**, *771*, 78–92; (k) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366–5412.
7. For recent applied MCRs using azomethine ylides, see: Craven, P.; Aimon, A.; Dow, M.; Fleury-Bregeot, N.; Guilleux, R.; Morgentin, R.; Roche, D.; Kalliokoski, T.; Foster, R.; Marsden, S. P.; Nelson, A. *Bioorg. Med. Chem.* **2015**, *23*, 2629–2635.
8. For multicomponent organocatalyzed examples, see: (a) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem.* **2007**, *119*, 5260–5262; (b) Ibrahem, I.; Ríos, R.; Vesely, J.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 6252–6257; (c) Yu, J.; He, L.; Chen, X.-H.; Song, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2009**, *11*, 4946–4949; (d) Iza, A.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E.; Martínez, J. I. *Org. Biomol. Chem.* **2010**, *8*, 2238–2244; (e) Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; Costa, P. R. R.; Crizanto de Lima, E.; Dias, A. G. *Synlett* **2010**, 962–966; (f) Chaulagain, M. R.; Aron, Z. D. J. *Org. Chem.* **2010**, *75*, 8271–8274; (g) Shi, F.; Luo, S.-W.; Tao, Z.-L.; Yu, J.; Tu, S.-J.; Gong, L.-Z. *Org. Lett.* **2011**, *13*, 4680–4683; (h) He, L.; Chen, X.-H.; Wang, D.-N.; Luo, S.-W.; Zhang, W.-Q.; Yu, J.; Ren, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2011**, *133*, 13504–13518; (i) Shi, F.; Tao, Z.-L.; Yu, J.; Tu, S.-J. *Tetrahedron: Asymmetry* **2011**, *22*, 2056–2064; (j) Shi, F.; Tao, Z.-L.; Luo, S.-W.; Tu, S.-J.; Gong, L.-Z. *Chem.—Eur. J.* **2012**, *18*, 6885–6894; (k) Shi, F.; Tao; Guo; Chang; Song, J.; Gong, L.-Z. *Org. Lett.* **2013**, *15*, 2676–2679; (l) Shi, F.; Xing, G.-J.; Tan, W.; Zu, R.-Y.; Tu, S.-J. *Org. Biomol. Chem.* **2013**, *11*, 1482–1489; (m) Zhu, R.-Y.; Wang, C.-S.; Jiang, F.; Shi, F.; Tu, S. J. *Tetrahedron: Asymmetry* **2014**, *25*, 617–624.
9. For multicomponent metal-catalyzed examples, see: (a) Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; Costa, P. R. R.; Crizanto de Lima, E.; Dias, A. G. *Synlett* **2010**, 962–966; (b) Mancebo-Aracil, J.; Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; Costa, P. R. R.; Crizanto de Lima, E.; Dias, A. G. *Tetrahedron: Asymmetry* **2012**, *23*, 1596–1606; (c) Chaulagain, M. R.; Felten, A. E.; Gilbert, K.; Aron, Z. D. *J. Org. Chem.* **2013**, *78*, 9471–9476.
10. (a) Calaza, M. I.; Cativiela, C. *Eur. J. Org. Chem.* **2008**, 3427–3448; (b) Companyó, X.; Alba, A. N.; Ríos, R. *Targets Heterocycl. Syst.* **2009**, *Vol. 13*, 147–174 Attanasi, O. A.; Spinelli, D. Eds. RSC, Cambridge; (c) *Privileged Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, 2011; (d) Nájera, C.; Sansano, J. M. *L'Actualité Chim.* **2013**, 28–30.
11. (a) Stecko, S.; Jurczak, M.; Urbanczyk-Lipkowska, Z.; Solecka, J.; Chmielewski, M. *Carbohydr. Res.* **2008**, *343*, 2215–2220; (b) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem.—Eur. J.* **2009**, *15*, 7808–7821.
12. (a) Grigg, R.; Jordan, M.; Malone, J. F. *Tetrahedron Lett.* **1979**, *20*, 3877–3878; (b) Faraji, L.; Arvinnezhad, H.; Alikami; Jadidi, N. K. *Lett. Org. Chem.* **2010**, *7*, 472–474; (c) Gorman, R. M.; Little, M. A.; Morris, J. A.; Sridharan, V. *Chem. Commun.* **2012**, 9537–9539.
13. In some examples proline itself has been generated from a previous 1,3-DC. For selected examples of racemic and non-racemic processes, see: (a) Cui, P.; Xu, L.; Shi, Z.; Gan, L. *J. Org. Chem.* **2011**, *76*, 4210–4213; (b) Codelli, J. A.; Puchlopek, A. L. A.; Reisman, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 1930–1933; (c) Lu, Q.; Song, G.; Jasinski, J. P.; Keeley, A. C.; Zhang, W. *Green Chem.* **2012**, *14*, 3010–3012; (d) Lim, A. D.; Codelli, J. A.; Reisman, S. E. *Chem. Sci.* **2013**, *4*, 650–654; (e) Sengupta, T.; Khamarui, S.; Samanta, S.; Maiti, D. K. *Chem. Commun.* **2013**, 9962–9964; (f) Mancebo-Aracil, J.; Nájera, C.; Sansano, J. M. *Chem. Commun.* **2013**, 11218–11220.
14. Mancebo-Aracil, J.; Nájera, C.; Sansano, J. M. *Org. Biomol. Chem.* **2013**, *11*, 662–675.
15. To date ethyl glyoxylate was employed as aldehyde together with ethyl *N*-(1-phenylethyl)glycinate, in thermal iminium route-1,3-DC affording a mixture of pyrrolidines with very low diastereoselections Wittland, C.; Flörke, U.; Risch, N. *Synthesis* **1997**, 1291–1295.
16. A new entry to azomethine ylides from glyoxals has been reported: Machamer, N. K.; Liu, X.; Waters, S. P. *Org. Lett.* **2014**, *16*, 4996–4999.
17. The enantioselective version of this multicomponent synthesis has been reported: Mancebo-Aracil, J.; Nájera, C.; Sansano, J. M. *Tetrahedron: Asymmetry* **2015**, *26*, 674–678.