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Graphical Abstract

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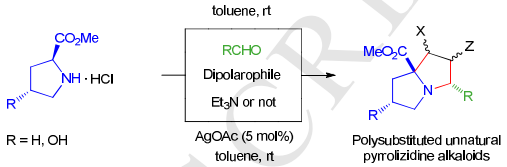

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Regio and diastereoselective multicomponent 1,3-dipolar cycloadditions between prolinate hydrochlorides, aldehydes and dipolarophiles for the direct synthesis of pyrrolizidines

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Dedicated to Prof. Richard Taylor on the occasion of his 65th birthday

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ABSTRACT

A general synthesis of highly substituted pyrrolizidines can be performed by a multicomponent 1,3-dipolar cycloaddition using proline ester hydrochlorides, aldehydes and dipolarophiles, at room temperature without catalysts or in the presence of AgOAc (5 mol%). In the case of (2*S*,4*R*)-4-hydroxyproline derivatives it is possible to obtain enantioenriched pyrrolizidines with high control of the regio- and diastereoselectivity affording the adducts 2,4-*trans*-2,5-*trans* according to an endo-approach and a S-dipole geometry of the in situ generated azomethine ylide. For proline esters a similar regioselectivity and endo-diastereoselectivity are observed when the dipole promotes an α-attack. However, when ethyl glyoxylate is used as aldehyde component the γ-attack of the S-ylide takes place preferentially giving rise the opposite regioselectivity for acrylic dipolarophiles, being crucial the role of silver acetate. In this case, the exo-adducts with a 2,3-*cis*-2,5-*trans* relative configuration are diastereoselectively obtained. In addition, computational studies have also been carried out to shed light on the origins of the diastereo- and regioselectivity observed for the described 1,3-dipolar cycloadditions.

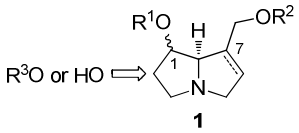
1. Introduction

The mechanisms of defense systems in plants are very complex. The diversification and evolution of secondary metabolites such as pyrrolizidine alkaloids (PAs) constitutes a clear example of the confrontation between plants and microorganisms/insects.[1] PAs are currently of special interest because several of them have been shown to cause toxic, genotoxic and carcinogenic reactions in humans when ingested with foods or herbal medicines.[2,3] Natural PAs are frequently hydroxylated, *O*-alkylated or *O*-acylated at key positions of the bicyclic heterocycle. Thus, for instance, the most common skeletal formula of retronecine (**1:** R^1, R^2 = H) has a hydroxyl group at the C1 whilst the hydroxymethyl group is bonded to the C7. On the other hand, some natural PAs bearing two hydroxy groups at 1- and 2-positions and a hydroxymethyl group at 7-position, such as (+)-crotanecine (**2**), madurensine (**3**) and anacrotine (**4**), isolated from crotalaria species, have been widely used for the treatment of bacterial and viral infections as well as for cancer.[4] A rare class of pyrrolizidines such as (+)-amphorogynines A (**5**) and D (**6**), characterized by substitution at C-2 by an hydroxyl group and a carboxylic group at C-7 were isolated from *Amphorogynine spicata* were also identified,[5] as well as the polyhydroxylated casuarine (**7**),[6] which was extracted from *Casuarina equisitefolia* (Figure 1). Non-hydroxylated natural pyrrolizidines shown in Figure 2 also exhibit potent glycosidase inhibition apart from other biological properties.[2]

The synthesis of all these alkaloids is not so simple, for example, (+)-**2** and (+)-**5**, have been prepared by diastereoselective [4+2] cycloadditions using nitroalkenes and a chiral vinyl ether,[4a,b] and by diastereoselective [2+2] dichloroketene-chiral enol ether cycloaddition,[6] respectively. Besides, (–)-**8** to (–)-**10** scaffolds were prepared by double

reductive amination[7] or through a biomimetic Mannich-type reaction,[8] or by metathesis.[9]

In order to facilitate their synthesis, several diastereoselective approaches to these heterocyclic frameworks have been successfully attempted. For instance, chain elongations of proline derivatives followed by cyclization,[10] transanular iodoamination[11] using lactams,[12] from other natural products,[13] etc. However, the most important and straightforward route is to employ a 1,3-dipolar cycloaddition (1,3-DC)[14,15,16] using mainly nitrones[17,18,19,20] or azomethine ylides.[21,22,23,24,25,26,27,28]



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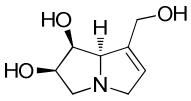
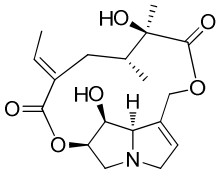
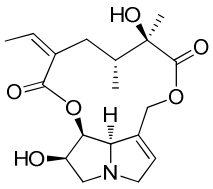


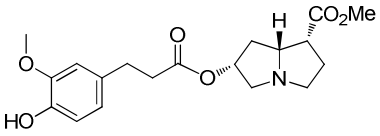
(+)-crotanecine **2**



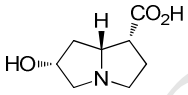
madurensine **3**



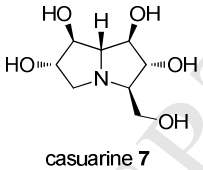
anacrotine **4**



(+)-amphorogynine A **5**

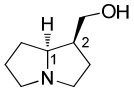


(+)-amphorogynine D **6**

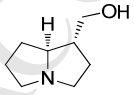


casuarine **7**

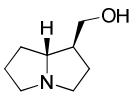
Figure 1. C6 or C2-hydroxylated pyrrolizidines.



(−)-isoretronecanol **8**



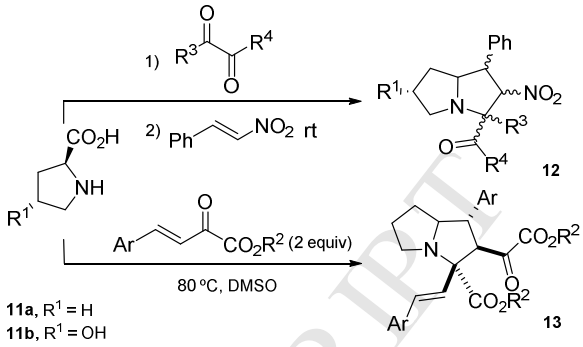
(−)-trachelantamidine **9**



(+)-laburnine **10**

Figure 2. Non-hydroxylated pyrrolizidine alkaloids.

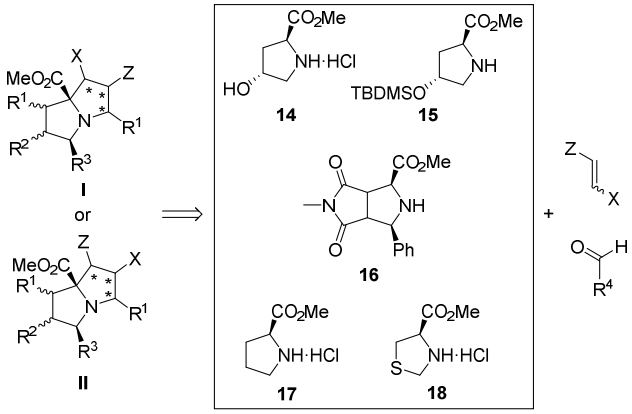
Felluga et *al*. described a three component decarboxylative 1,3-DC using proline **11a** or (2*S*,4*R*)-4-hydroxyproline **11b** and 2,3-butanedione or ethyl pyruvate with β-nitrostyrene to give, at room temperature, a mixture of diastereomeric pyrrolidines **12** in good yields (78-90%) (Scheme 1).[25] More recently, it has been found that proline **11a** itself underwent a domino iminium salt formation with α,β-unsaturated β-keto esters followed by decarboxylation and diastereoselective cycloaddition with the named keto ester at 80 ºC in DMSO as solvent, to give regio- and diastereoselectively **13** in good chemical yields (80-90%) (Scheme 1).[25]



11a, R^1 = H
11b, R^1 = OH

Scheme 1. Pyrrolizidine synthesis from azomethine ylides generated by decarboxylation of prolines.[25,26]

According to all these features, azomethine ylides derived from enantiomerically enriched commercially available (2*S*,4*R*)-4-hydroxyproline **14**,[26] or its *t*-butyldimethylsilyl derivative **15**,[26] synthetic enantiomerically enriched polysubstituted proline surrogate **16**, or even proline **17**[26,27] or 4-thiaproline **18** methyl ester hydrochlorides, and aldehydes were envisaged to undergo diastereoselective cycloadditions with electrophilic alkenes providing the pyrrolizidine nucleus. In this work the scope of the synthesis of non-natural pyrrolizidine alkaloids **I** or **II** employing this multicomponent diastereoselective 1,3-DC of azomethine ylides, prepared *in situ* following a non-decarboxylative iminium route by reaction of **14**-**18** with aldehydes will be described (Scheme 2). We will also take in consideration several computational studies for the clarification and rationalization of the high diastereoselection observed in the most representative transformations.



I
or
II

14 **15** **16** **17** **18**

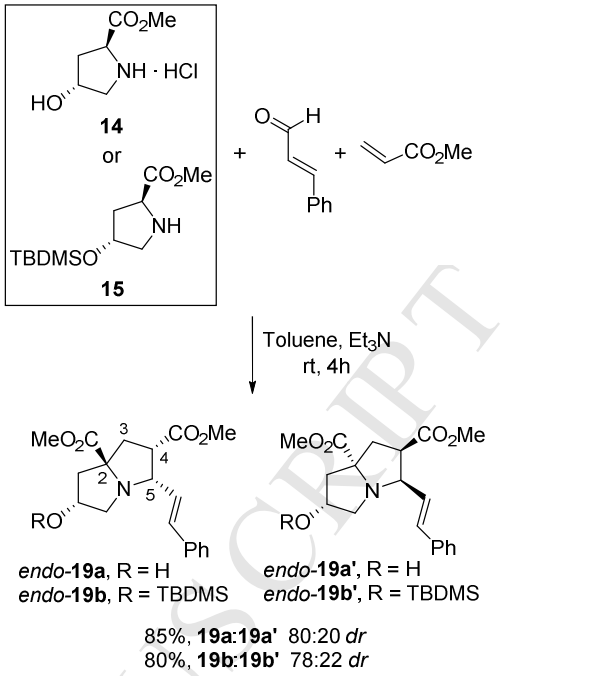
Scheme 2. Retrosynthetic analysis of pyrrolizidines prepared in this work by multicomponent 1,3-DC.

2. Results and Discussion

2.1. Multicomponent 1,3-DC with enantiomerically enriched (2S,4R)-4-hydroxyproline methyl ester hydrochloride 14, with its derivative 15, and cycloadduct 16

When the multicomponent 1,3-DC involving (2*S*,4*R*)-4-hydroxyproline methyl ester hydrochloride **14** was performed employing cinnamaldehyde, as iminium precursor, and methyl acrylate as dipolarophile, in toluene with 1 equiv. of triethylamine at room temperature, the reaction took place in 4 h obtaining 85% yield of a 80:20 mixture of compounds *endo*-**19a** and *endo*-**19a'** (Scheme 3). These reaction conditions were initially settled due to the previous experience gained from other multicomponent 1,3-cycloadditions published by our group.[27,29,30] The employment of other different solvents such as DCM, or THF at room temperature gave lower diastereoselection. The introduction of a bulkier protecting group at the hydroxy functionality was carried out onto molecule **14** to give **15** with the aim to study the diastereoselection of the corresponding reaction product *endo*-**19b**,[31] but the final diastereomeric ratio of *endo*-**19b**:*endo*-**19b'** was slightly lower (78:18 dr, Scheme 3).

In light of the absolute configuration of the major 2,4-*trans*-2,5-*cis*-diastereoisomers **19**, which were unambiguously established after X-ray diffraction analysis of *endo*-**19a**,[27] it can be deduced that a preferential α-attack of the less sterically hindered S-shape dipole A occurred (Figure 3).The approach of the acrylate took place in an *endo*-manner and by the same face where the hydroxy group is located (Scheme 3). Comparative nOe, and bidimensional experiments and analysis of the corresponding coupling constants confirmed the proposed structure also for the minor pyrrolizidines **19'**, in this case the acrylate reacting by the opposite face to give **19a'** with a 2,4-*trans*-2,5-*trans*-relative configuration. The observed 2,5-*trans* arrangement is in agreement with a S-shape dipole A, which is more stable than the U-shape one **A** (Figure 3).[32] This last intermediate would afford the 2,5-*cis* relative configuration. The stereochemical results are very different to those observed for the 1,3-DC of acyclic dipoles generated from imino esters, which gave, through a W-shape conformation 2,5-*cis* substituted *endo*-prolines **III** (Figure 4).[33] Chemical shifts in ^{1}H NMR and coupling constants are very similar between **19** and **19'** but there is a very important nOe $H_{C5} \rightarrow CO_2Me$ bonded to the quaternary centre in both molecules.



Scheme 3. Multicomponent 1,3-DC of cinnamaldehyde and methyl acrylate with (2*S*,4*R*)-4-hydroxyproline methyl ester hydrochlorides **14** and its TBDMS surrogate **15**.

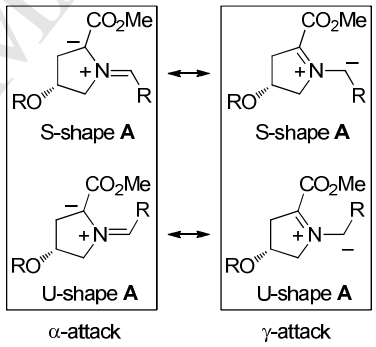


Figure 3. Intermediate 1,3-dipoles **A** derived from (2*S*,4*R*)-4-hydroxyproline methyl ester **14** and **15**.

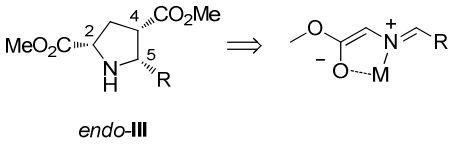
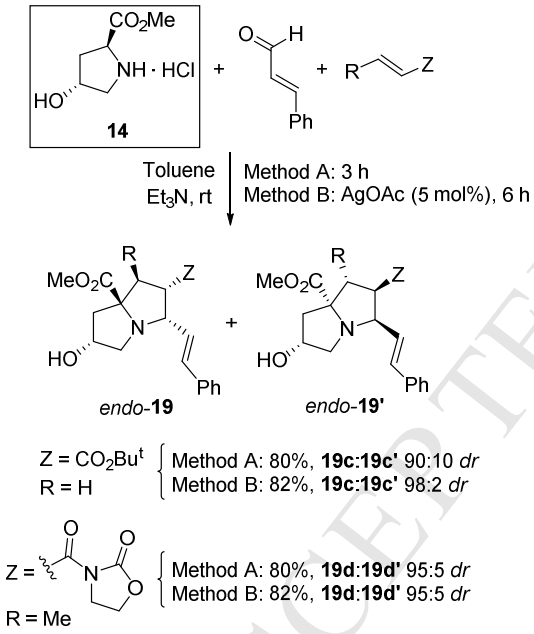


Figure 4. Prolines derived from a 1,3-DC of acyclic imino esters.

The study of the general scope and the increment of the diastereoselection moved us to test several acrylic derivatives maintaining the aldehyde structure. Thus, the incorporation of *tert*-butyl acrylate instead of methyl acrylate produced an increment of the diastereoselection (90:10 dr) of the product *endo*-**19c** (Scheme 4), which was isolated in 80% yield after flash chromatography. Besides, the *dr* could be improved to a 98:2 when the reaction was catalyzed with silver acetate (5 mol%) and the corresponding product **19c** was isolated (82% yield) in enantiomerically pure form.

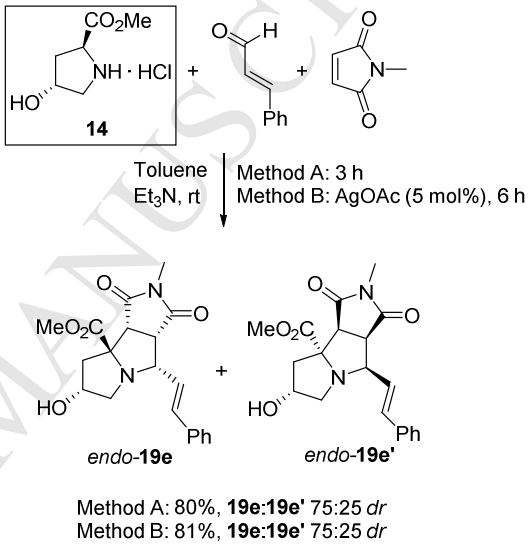
(*E*)-3-(But-2-enoyl)oxazolidin-2-one was also tested as dipolarophile and the diastereoselection was even higher obtaining up to 95:5 *dr* for *endo*-**19d** independently of the method A or B employed (Scheme 4). Thus, cycloadducts *endo*-**19c** and *endo*-**19d** can be isolated as optically pure enantiomers. In these two examples the *endo*-selectivity was almost complete and the regiochemistry of the process followed the same pattern discussed previously for the reaction involving alkyl acrylates. The assignment of the absolute configuration of the major compounds *endo*-**19c** and *endo*-**19d** was done by analogy to compound **19a** because its CHN signal in ^{1}H NMR is slowly shifted (0.1-0.2 ppm) at lower fields than the identical signal of the compound **19a'**.



Scheme 4. Multicomponent 1,3-DC between (2*S*,4*R*)-4-hydroxyproline methyl ester hydrochloride **14**, cinnamaldehyde and α,β-unsaturated compounds.

In contrast, *N*-methylmaleimide gave a lower diastereoselection when using (2*S*,4*R*)-4-hydroxyproline methyl ester hydrochloride **14** as starting material. In this reaction pyrrolizidines *endo*-**19e** and *endo*-**19e'** were isolated in 80-81% yield and 75:25 *dr* by using both A and B methods (Scheme 5). The presence of both diastereoisomers can be explained by the corresponding α-attack of the S-shape dipole **A** by both faces (Figure 3). The interest of these fused tricyclic pyrrolizidines containing the maleimide residue was demonstrated in a series of publications dealing with analogous skeletons inhibitors of thrombin.[34]

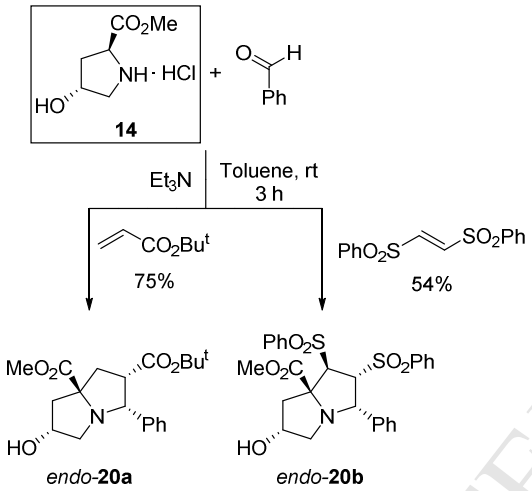
Again, the structure of major compounds *endo*-**19e** *versus* *endo*-**19e'** was was confirmed by the lower field shift of CHN signal in ^{1}H NMR.



Scheme 5. Multicomponent 1,3-DC between (2*S*,4*R*)-4-hydroxyproline methyl ester hydrochloride **14**, cinnamaldehyde and NMM.

With respect to the effect of Lewis acids such as $Ti(OPr^i)_4$, $ZnCl_2$, and AgOAc in the diastereoselection of the overall process either activating the dipolarophile or forming the silver enolate in the dipole was investigated. Only AgOAc was able to promote the reaction generating very clean reaction products *endo*-**19**. To understand the effect of the silver salt, a parallel study was undertaken. In all transformations the results of the cycloadditions run in the presence of silver acetate were compared with the analogous reactions performed without it. As it was mentioned (above), an improvement of the diastereomeric ratio was observed in the reaction where *tert*-butyl acrylate was the selected dipolarophile. In this example, compound **19c** was isolated in good chemical yield (82%) and 98:2 *dr* (Scheme 4). Reactions involving *N*-alkenoyl oxazolidinone and NMM did not reveal any variation of diastereoselection when working in the presence of 5 mol% of silver acetate (Scheme 4 and 5). In both silver-catalyzed and non-catalyzed processes the crude reaction mixtures of diastereoisomers were very clean (^{1}H NMR spectroscopy) and isolated yields were excellent as it was shown in Schemes 4 and 5.

When benzaldehyde, instead of cinnamaldehyde, was allowed to react with (2*S*,4*R*)-hydroxyproline methyl ester hydrochloride **14** and *tert*-butyl acrylate *endo*-**20a** (>99:1 dr) as unique product was obtained in 75% yield (Scheme 6). Polysubstituted pyrrolizidine *endo*-**20b**, obtained through the same process but using (*E*)-1,2-bis(phenylsulfonyl)ethylene (BPSE) as dipolarophile, was isolated in moderate 54% yield as only one stereoisomer as well (Scheme 6). The effect of the addition of silver acetate (Method B) was only tested in the multicomponent cycloaddition involving the disulfone with the aim to increase the yield, but any improvement was observed. Again, the prevalence of the α-attack of the corresponding S-shape dipole **A** (Figure 3) was the driving force of the generation of pure *endo*-stereoisomers **20**, the dipolarophile being approached by the same face where the hydroxy group is located. The assignment of the absolute configuration of the major compounds *endo*-**20** done by the intensity of the nOe $H_{C5} \rightarrow CO_2Me$ bonded to the quaternary centre in both molecules following the same approach observed for molecules **19a**.



Scheme 6. Multicomponent 1,3-DC of (2*S*,4*R*)-4-hydroxyproline methyl ester hydrochloride **14**, benzaldehyde and different dipolarophiles.

Attempts to introduce an aliphatic aldehyde such as ethyl glyoxylate using both methods, were unfruitful. On the other hand, when **14**, triethylamine, isovaleraldehyde, and *tert*-butyl acrylate were allowed to react in toluene only the Michael-type addition adduct **21** (Figure 5) was obtained in 84% yield.

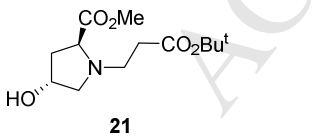
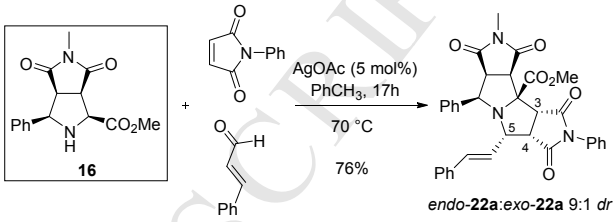


Figure 5. Michael-type adduct **21** isolated in the reaction of **14** with isovaleraldehyde and *tert*-butyl acrylate.

Analogously, optically pure polysubstituted proline methyl ester derivative **16**, obtained according to the literature using a chiral binap·silver(I) perchlorate complex,[35] was also appropriate to complete the titled multicomponent 1,3-DC with NPM and cinnamaldehyde at 70 ºC. In this reaction the 9:1 *endo*-**22a**:*exo*-**22a** ratio was isolated in 76% chemical yield (Scheme 7). The presence of both substituents at 2- and 5-positions of the starting proline derivative **16** avoided the approach of the aldehyde when the reaction was carried out at room temperature, so a higher one (70 ºC) is needed. The detection of the major *endo*-isomer and a small amount of the *exo*-adduct was also possible by the analysis of the crude ^{1}H NMR spectra. The relative configuration of all products obtained and described in this section was established according to nOe experiments, especially crucial being the intensity of the nOe of the three H_{C5} H_{C4} $H_{C3} \rightarrow CO_2Me$ bonded to the quaternary centre.



Scheme 7. Multicomponent 1,3-DC of enantiomerically enriched prolinate methyl ester **16** with benzaldehyde and NPM.

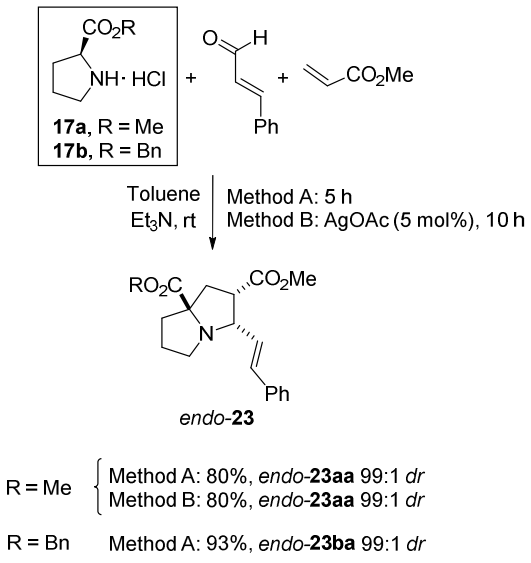
Absolute or relative configurations of all products were assigned on the basis of X-ray diffraction analysis (for a small number of molecules, see text), and NMR experiments (see supporting information).

2.2. Multicomponent 1,3-DC with proline ester hydrochlorides 17 and 4-thiaproline 18

The synthesis of pyrrolizidines **23** was initially tested at room temperature employing an analogous multicomponent process as described in the previous section. In this case, (*S*)-proline methyl ester hydrochloride **17a** was allowed to react with cinnamaldehyde and methyl acrylate in the presence of triethylamine (1 equiv). Although the reaction was slower in toluene (5 h) than in DCM or THF with methyl acrylate, pure **23aa** (^{1}H NMR) was obtained in 96% yield. Therefore, this solvent was selected again because a higher diastereoselection (99:1) was obtained than with DCM or THF (Scheme 8). In this transformation the presence of the benzyl or methyl ester in the starting proline was not very noticeable in terms of the final diastereoselection, although *endo*-**23ba** was obtained in a higher 93% yield (Scheme 8). The presence of the silver salt (method B) afforded analogous results than the reaction performed without metal catalysis.

Based on the X-ray diffraction analysis of molecule *endo*-**23aa**,[26] we could justify its formation through a preferential α-attack of the less sterically hindered S-shape dipole **B** (Figure 6). The approach of the acrylate took place in an *endo*-manner such as it was described in the reactions performed with the enantiomerically pure 4-hydroxyproline derivative **14**. Also, in this case, nOe, and bidimensional experiments and analysis of the corresponding ^{1}H NMR coupling constants confirmed the proposed structure for these compounds *endo*-**23**. This preference of the *trans*-2,5-relative configuration (according to the same

proline **III** nomenclature, Figure 4) was also confirmed for these multicomponent transformations.



Scheme 8. Multicomponent 1,3-DC of proline ester hydrochlorides **17**, cinnamaldehyde and methyl acrylate.

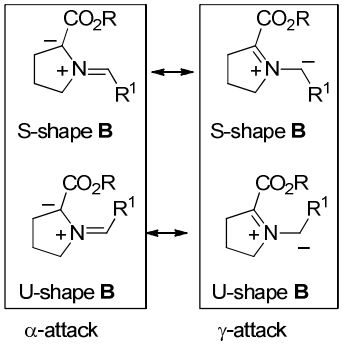
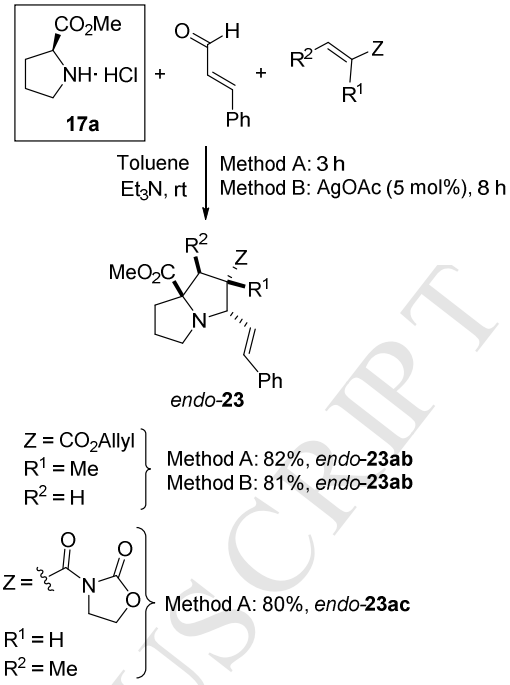


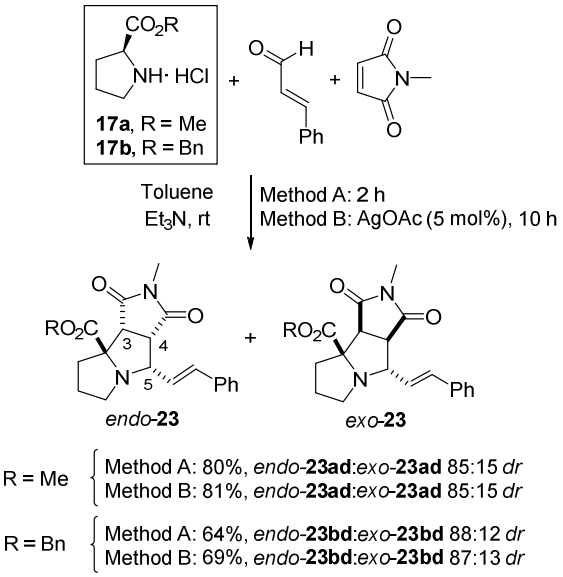
Figure 6. Intermediate 1,3-dipoles **B** derived from proline esters **17**.

The study of the presence of α- or β-substituents in the acrylate moiety was carried out employing allyl methacrylate and (*E*)-3-(but-2-enoyl)oxazolidin-2-one, respectively. Both dipolarophiles afforded pyrrolizidines **23ab** and **23ac** as unique diastereoisomers in excellent chemical yields (Scheme 9). The role of silver acetate was negligible and the position of the substituents of acrylates did not produce any significant steric hindrance. The assignment of the relative configuration of the major racemic form **23ab** and **23ac** was done according to the chemical shift of the CHN signal (≥4.2 ppm). Unfortunately, the intensity of the nOe H_{C5}→CO_2*Me* bonded to the quaternary centre was very weak, nevertheless an important nOe was detected in H_{C5}→*Me* of each cycloadduct.



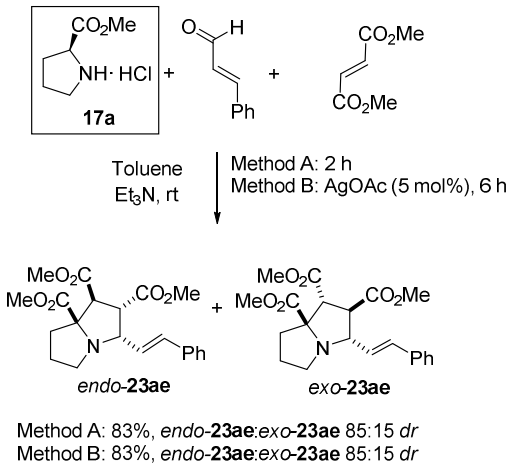
Scheme 9. Multicomponent 1,3-DC of proline methyl ester hydrochloride **17a**, cinnamaldehyde and α,β-unsaturated carbonyl compounds.

When NMM was tested with both methyl and benzyl prolinates, after 2 h of reaction time, a similar *dr* was obtained, but compounds *endo*-**23ad** and *exo*-**23ad** were isolated as cleaner crude products (^{1}H NMR spectroscopy) than the reaction involving proline **17b** (Scheme 10). According to precedent results, the *endo*-approach through the α-attack promoted by S-shape dipole **B** (Figure 6) was preferred in all cases assayed. In the case of final cycloadducts **23ad** and **23bd** the chemical shift CHN signal (≥4.3 ppm) corresponded to the *exo*-adduct, presumably due to the more restricted fused-tricyclic skeleton. The intensity of the nOe H_{C5}→CO_2*Me* and nOe H_{C5}→CO_2CH_2 was noticeable, and also very high increment of population was detected in H_{C6} upon irradiation of H_{C5} atom in both molecules.



Scheme 10. Multicomponent 1,3-DC of proline ester hydrochlorides **17**, cinnamaldehyde and NMM.

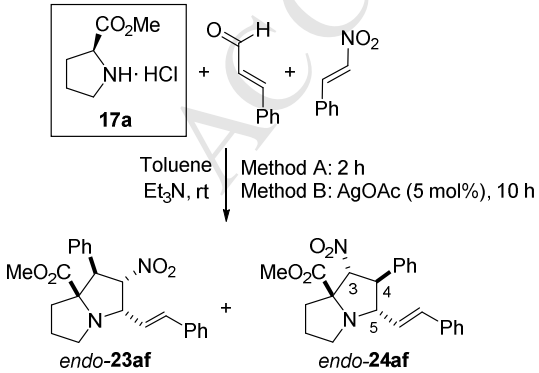
Dimethyl fumarate offered a similar behavior in terms of diastereoselectivity (85:15) and chemical yields (83%). By using methods A and B, the most stable *endo*-**23ae** was the major diastereoisomer according to an *endo*-approach (Scheme 11).[36] For racemic form *endo*-**23ae** the chemical shift of the CNH signal was 4.3 ppm whilst for the minor *exo*-adduct was 4.1 ppm. In this mixture, nOe experiment was not useful.



Method A: 83%, *endo*-**23ae**:*exo*-**23ae** 85:15 *dr*
Method B: 83%, *endo*-**23ae**:*exo*-**23ae** 85:15 *dr*

Scheme 11. Multicomponent 1,3-DC of proline methyl ester hydrochloride **18a**, cinnamaldehyde and dimethyl fumarate.

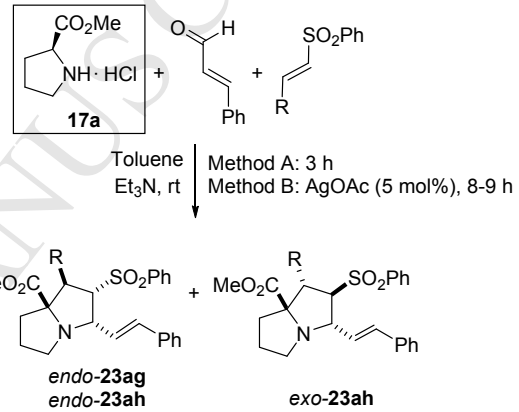
On the other hand, when β-nitrostyrene was employed as dipolarophile, together with proline methyl ester hydrochloride **17a** and cinnamaldehyde, a different regio and stereochemical outcomes were observed. The major *endo*-cycloadduct **23af** was obtained with regioisomer **24af** (85:15 *rr*), which could be isolated in 79% and 10% yield, respectively (Scheme 12). A plausible explanation for the formation of this new regioisomer (not detected with other dipolarophiles) can be attributed to the lowest LUMO energy and high reactivity of the nitroalkene, which was able to trap the small amount of the S-shape dipole **B** reacting by its γ-position (Figure 6). ^{1}H NMR spectra of *endo*-cycloadduct **23af** shown CHN signal at 4.8 ppm and $CHNO_2$ at 6.1 ppm. A very intense nOe effect was observed between these two hydrogen atoms (15% aprox.), and a positive small nOe H_{C5} H_{C4} $Ph_{C3}\rightarrow CO_2Me$. In regioisomer **24af** $H_{C3}\rightarrow CO_2Me$ and $H_{C3}\rightarrow H_{C5}$ positive nOe were observed.



Method A: *dr* 85:15; isolated yield: **23af** 79%, **24af** 10%
Method B: *dr* 85:15; isolated yield: **23af** 78%, **24af** 10%

Scheme 12. Multicomponent 1,3-DC of proline methyl ester hydrochloride **17a**, cinnamaldehyde and β-nitrostyrene.

Phenyl vinyl sulfone furnished one diastereoisomer *endo*-**23ag** in 71% with a small amount o other stereoisomer (Scheme 16), whilst BPSE gave a very complex reaction mixture of products, from which *endo*-**23ah** and *exo*-**23ah** could be isolated in 69% overall yield (Scheme 13). The presence of the silver acetate (5 mol%) made the reactions slower giving the same results. The regio- and stereochemistry of the processes involving alkenyl sulfones followed the general pattern of reactivity controlled by α-attack of the S-shape dipole **B** (Figure 6). In the reaction dealing with BPSE an additional non-identified cycloadduct (ca. 19%) was observed in the crude NMR spectra which could not be isolated after flash chromatography. The relative configuration was established according to the results given by nOe experiments.

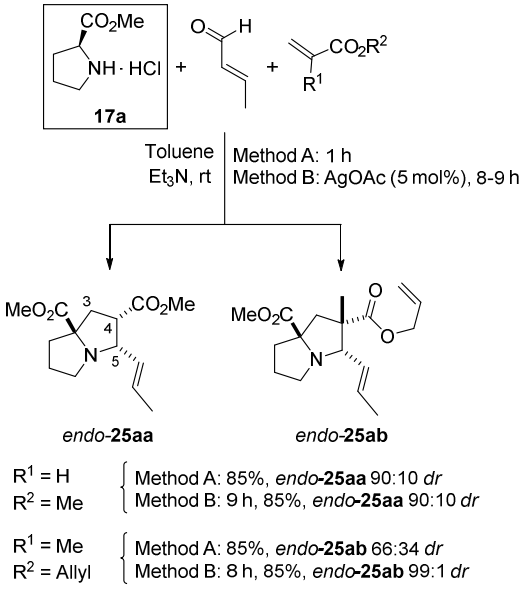


R = H
Method A: 71%, *endo*-**23ag** 99:1 *dr*
Method B: 8 h, 69%, *endo*-**23ag** 99:1 *dr*

R = SO_2Ph
Method A: 85%, *endo*-**23ah**:*exo*-**23ah** 78:12 *dr*
Method B: 9 h, 72%, *endo*-**23ah**:*exo*-**23ah** 72:28 *dr*

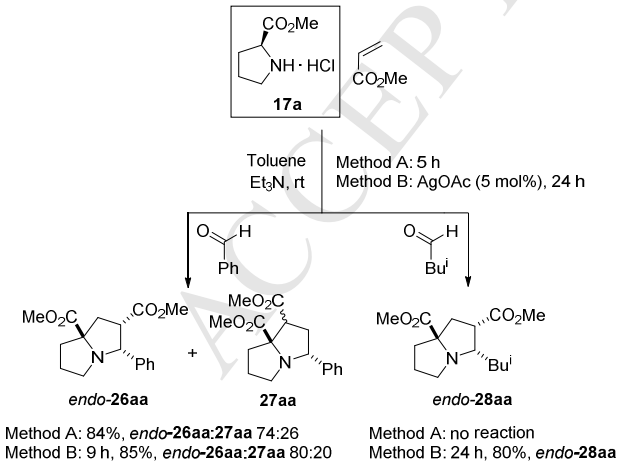
Scheme 13. Multicomponent 1,3-DC of proline methyl ester hydrochloride **17a**, cinnamaldehyde and vinyl sulfones.

The use of crotonaldehyde instead of cinnamaldehyde in the multicomponent reaction of **17a** together with acrylates was evaluated. In general, the α-attack of the dipole was preferred. Methyl acrylate did not give as good diasteresoselectivity for *endo*-**25aa** (Scheme 14) than in the case of using cinnamaldehyde (Scheme 9). However, a very important difference was found when allyl methacrylate was attempted. Here, when method A was attempted the reaction gave a poor diastereoselection but the presence of AgOAc gave rise to an excellent *endo*-diastereoselectivity (98%) of the pyrrolizidine *endo*-**25ab**, which was isolated in 85% yield (Scheme 14). Again, H_{C5} $H_{C4}\rightarrow CO_2Me$, $H_{C4}\rightarrow H_{C5}$ and $H_{C5}\rightarrow$Me positive nOe were crucial for the assignment of the relative configuration not only for cycloadducts **25**, but for pyrrolizidines *endo*-**26** and *endo*-**28**.



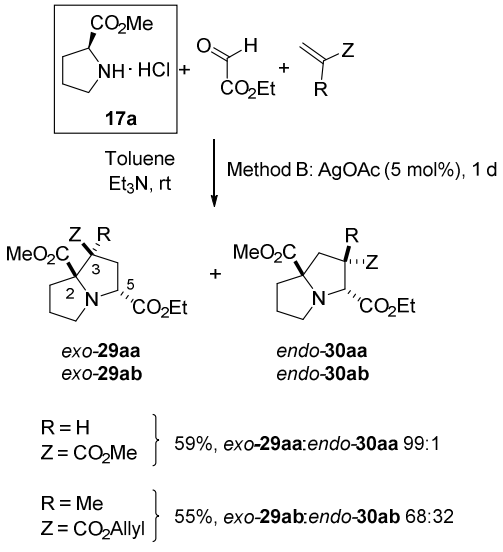
Scheme 14. Multicomponent 1,3-DC of proline methyl ester hydrochloride **17a**, crotonaldehyde and α,β-unsaturated esters.

Benzaldehyde induced the formation of the expected *endo*-**26aa** but also the corresponding unidentified regioisomer **27aa** through the described α- and γ-attack relative to S-shape **B** dipole, respectively (Figure 6) in both silver-catalyzed and non-catalyzed processes involving proline ester **17a** and methyl acrylate. In these two examples the conversion and chemical yield of compound **26aa** were similar independently of the method employed (Scheme 15). By contrast, isovaleraldehyde derived ylide reacted exclusively through an α-attack of the S-shape **B** dipole (Figure 6), giving access to pyrrolizidine *endo*-**28aa** and other non-identified byproducts only in the presence of silver acetate (Scheme 15).



Scheme 15. Multicomponent 1,3-DC of proline methyl ester hydrochoride **17a**, benzaldehyde or isovaleraldehyde and methyl acrylate.

According to the experience acquired in this type of multicomponent reaction using acyclic α-amino esters, dipolarophiles and ethyl glyoxylate,[29] we used this aldehyde for the synthesis of more functionalized pyrrolizidines **29** and **30** (Schemes 16 and 17). The domino process took place exclusively under silver-promoted catalysis in 1 d at room temperature in all examples tested, otherwise the reaction completely failed. The domino sequence involving acrylates afforded relevant outcomes. When methyl acrylate was used compound *exo*-**29aa** was isolated as only one regio- and diastereoisomer in 59% yield (Scheme 16). The same *exo*-**30ab** product was the major isolated regio- and diasteroisomer when the reaction was performed with allyl methacrylate. In this example, the *endo*-cycloadduct **29ab** (until now, the most favored cycloadduct in precedent reactions with conjugated, aromatic and aliphatic aldehydes) was also generated but in lower proportions (Scheme 17). An explanation for justifying the driving force responsible of the observed regioselectivity in these particular examples can be due to the presence of the ethoxycarbonyl group incorporated during the formation of the iminium salt. This electron withdrawing group competed with the methoxycarbonyl unit of the starting proline ester in the stabilization of the negative charge of the dipole **C** (Figure 7). The highest stability of the inner ring double bond in dipoles **C**, with respect to the outer ring alkene, allowed a preferential γ-attack of the named dipole affording a 2,5-*trans*-relative configuration of both ester groups via the γ-attack of the less sterically hindered S-shape dipole **C** (Figure 7). Besides, the *exo*-approach occurred because a stereoelectonic effect between both ester groups of the dipolarophile and proline components partially avoided the endo-approach.[29] This last hypothesis can be supported by the result generated from the cycloaddition using allyl methacrylate. In this way, allyl ester favored in lesser extension the generation of *exo*-**29ab** giving a larger amount of *endo*-**30ab**. Both positive $H_{C5}\rightarrow CO_2Me$ bonded to the quaternary C_2 and $CO_2Me\rightarrow CO_2Me$ nOe effects and negative $H_{C3}\rightarrow H_{C5}$ or $Me_{C3}\rightarrow H_{C5}$ justified the proposed relative configuration for pyrrolizidine *exo*-**29a**.



Scheme 16. Multicomponent 1,3-DC of proline methyl ester hydrochloride **17a**, ethyl glyoxylate and acrylates.

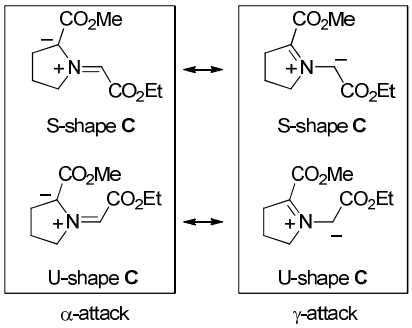
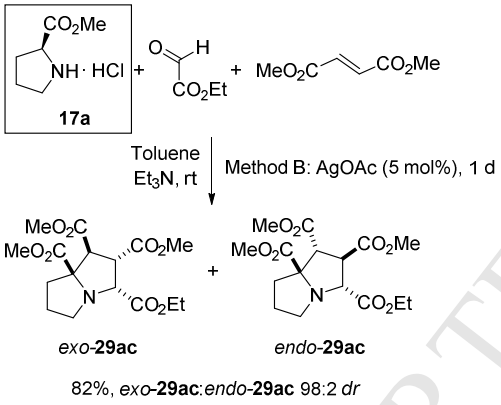


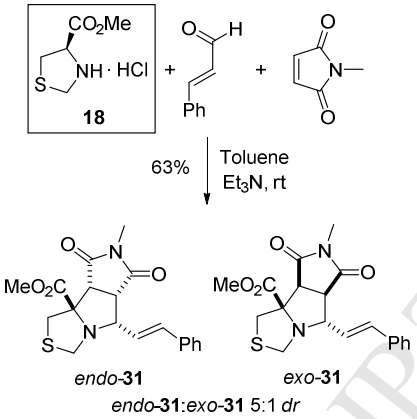
Figure 7. Intermediate 1,3-dipoles **C** derived from proline ester **17a** and ethyl glyoxylate.

Under the same reaction conditions, dimethyl fumarate afforded compounds *exo*-**29ac** and *endo*-**29ac** in 82% yield and with a high regioisomeric ratio (98:2, Scheme 17). This result also supported the explanation given above for the reaction of proline methyl ester, ethyl glyoxylate and acrylates. NOESY experiment, together with another bidimensional NMR spectra helped us to discard the *endo*-**29ac** relative configuration corresponding to the major isolated product.



Scheme 17. Multicomponent 1,3-DC of proline methyl ester hydrochloride **17a**, ethyl glyoxylate and dimethyl fumarate.

The study of the scope of these transformations was finished testing 4-thiaproline methyl ester hydrochloride **18** as dipole precursor together with cinnamaldehyde and NMM. The result of this reaction performed at room temperature was satisfactory giving a 63% yield of a 5:1 *endo*-**31**:*exo*-**31** *dr* (Scheme 18). The positive nOe $H_{C5} \rightarrow H_{C4}$ H_{C3} CO_2Me allowed us to assign the drawn structure for cycloadduct *endo*-**31**.



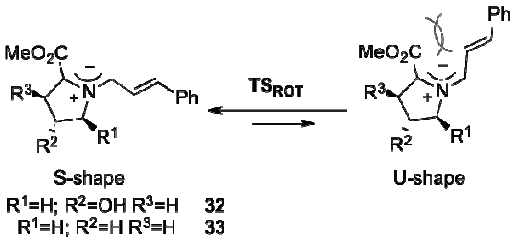
Scheme 18. Multicomponent 1,3-DC of 4-thiaproline methyl ester hydrochloride **18**, cinnamaldehyde and NMM.

2.3 Computational studies

In order to further understand and rationalize the high diastereoselectivity observed experimentally in the multicomponent [3+2] reactions described in this work, we decided to perform several DFT calculations. As model case studies, we selected the reaction between cinnamaldehyde, NMM and the selected proline derivatives **14**, and **17a**. In addition, the diverse regioselectivity observed on the reaction of cinnamaldehyde, **17a** and β-nitrostyrene as dipolarophile was also analyzed.

Analysis of the azomethyne ylides derived from cinnamaldehyde and 14 or 17a. Initially, we analyzed the S-shape and U-shape related to the isomerization processes of the 1,3-dipoles s-**32** and s-**33** derived from cinnamaldehyde and the proline esters **14** or **17a**, respectively. The results are collected in Table 1 and Figure 8.

Table 1. Activation and reaction Gibbs free energies associated with the isomerization processes of S- and U-shaped azomethine ylides **32** and **33** derived from cinnamaldehyde and proline derivatives **14** or **17a**, respectively. Values computed at M06-2X(PCM)/def2-TZVPP//B3LYP(PCM)/6-31G* level of theory.



entry	Compound	Proline derivative	ΔG^a (kcal mol^{-1})	ΔG_{RXN} (kcal mol^{-1})
1	s-**32**	**14**	+32.3	+2.3
2	s-**33**	**17a**	+31.4	+0.5

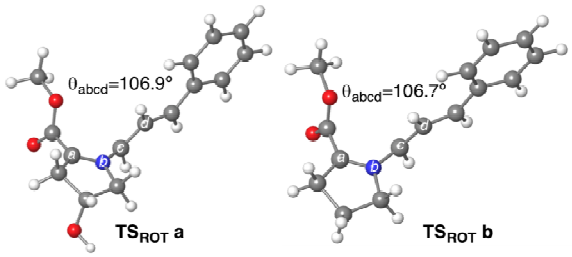


Figure 8. Main geometrical features of the transition structures associated with the isomerization of s-**32** (TS_{ROT}a) and s-**33** (TS_{ROT}b) computed at B3LYP (PCM) /6-31G* level of theory. Dihedral angles (θ_{abcd}, absolute value), are in deg.

These calculations indicated that the isomerization processes of s-**32** and s-**33** azomethine ylides present an activation barrier higher than 30 kcal mol^{-1}, which is unreachable at room temperature. Moreover, the U-shaped azomethine ylides are less stable than their S-shaped counterparts due to steric clash between cinnamaldehyde chain and ester moieties. On the basis of these results, we concluded that formation of u-**32** or u-**33** is neither kinetically nor thermodynamically favored. Therefore, only S-shaped azomethine ylides will be considered in the next calculations.

We also analyzed the frontier molecular orbitals (FMO) of s-**32** and s-**33**. In this manner, it is feasible to understand the preference for α- or γ-attacks experimentally observed (Figure 9).

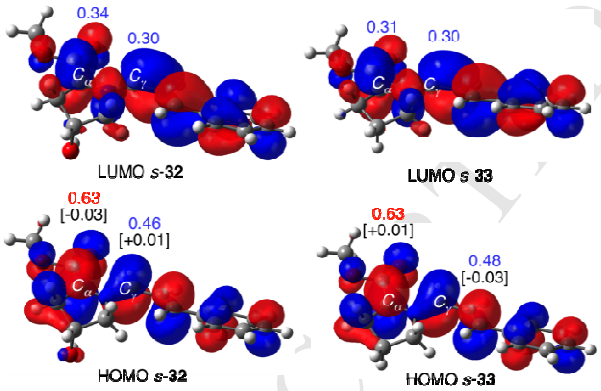
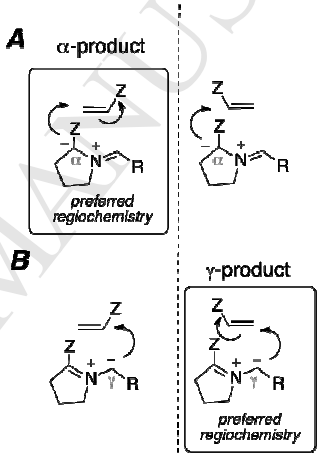


Figure 9. Frontier molecular orbitals (FMO) and NBO charges (in brackets) of azomethine ylides s-**32** and s-**33** computed at the B3LYP/6-31G* level of theory. Expansion orbital coefficients on C_α and C_γ atoms computed at RHF/AM1 level are also included.

The computed FMO of azomethine ylides s-**32** and s-**33** are quite similar in shape. The analysis of the atomic expansion coefficients in the relevant FMO revealed no significant differences between both ylides. Moreover, in all cases, the expansion coefficient on C_α is higher than on C_γ. It is well known that in a concerted 1,3-DC reaction, the cyclic electronic circulation requires the participation of two stabilizing interactions between the relevant FMO of the azomethine ylides and the dipolarophiles, namely $HOMO_{ylide}$-$LUMO_{dipolarophile}$ and $HOMO_{dipolarophile}$-$LUMO_{ylide}$.[37] In the case of unsymmetrical dipolarophiles, the product with the maximum orbital overlap, that is, the α-product, will be formed due to a favored cyclic electronic circulation.[38] Therefore, a similar preferential regioselectivity in the [3+2] cycloadditions can be expected for s-**32** and s-**33** ylides, since the atomic expansion coefficients are almost equal for a given atom.

If we assume an stepwise 1,3-DC reaction, the accepted mechanism consists of an addition of the 1,3-dipole on the dipolarophile to form a zwiterionic intermediate, followed by a ring closure step. Thus, in the case of non-symmetrical dipolarophiles, the negatively charged carbon atom of the azomethine ylide would preferentially react in the first step with the dipolarophile in a Michael-like fashion. The computed NBO charges on C_α and C_γ are different in the selected azomethine ylides. In the case of s-**32**, the negative charge is placed on C_α, whereas in s-**33** it is placed on C_γ. Therefore, electrostatic arguments point to different regioselectivities for s-**32** and s-**33** (Scheme 19).



Scheme 19. Preferred regiochemistry expected on the 1,3-DC of azomethine ylides considering the initial Michael-like first step of an stepwise mechanism where the negative charge is placed on (A) C_α (α-attack) or (B) C_γ (γ-attack). Z represents an electron-withdrawing group.

In the case of azomethine ylide s-**32**, both scenarios predict the exclusive formation of the α-attack, in good agreement with the experimental results. On the other hand, in the case of s-**33**, the preference for the possible attacks results from a compromise between the effective orbital overlap between reagents associated with a pericyclic concerted mechanism, which favors the α-attack, and the unsymmetrical electron density distribution on C_α and C_γ in the azomethine ylides which favors the γ-attack. This observation is in good agreement with the low regioselectivity observed in the experimental reaction of s-33 with β-nitrostyrene (Scheme 12).

Multicomponent 1,3-DC of cinnamaldehyde, NMM and 14 or 17a. We also computed all the stationary points associated with the cycloaddition reaction between NMM and s-**32** or s-**33**. The results are collected in Table 2 and Figure 10.

Table 2. Computed activation and reaction Gibbs free energies of the [3+2] cycloadditions of S-shaped azomethine ylides s-**32** and s-**33** with NMM at M06-2X(PCM)/def2-TZVPP//B3LYP(PCM)/6-31G* level of theory.

entry	ylide		cycloadduct	ΔG^a (kcal mol^{-1})	ΔG_{RXN} (kcal mol^{-1})
1	s-**32**	*endo*	*endo*-**19e**	+4.1	-29.8
2		*endo'*	*endo*-**19e'**	+7.8	-30.0
3		*exo*	*exo*-**19e**	+11.3	-30.3
4		*exo'*	*exo*-**19e'**	+9.8	-30.3
5	s-**33**	*endo*	*endo*-**23ad**	+5.0	-30.6
6		*exo*	*exo*-**23ad**	+6.4	-29.8

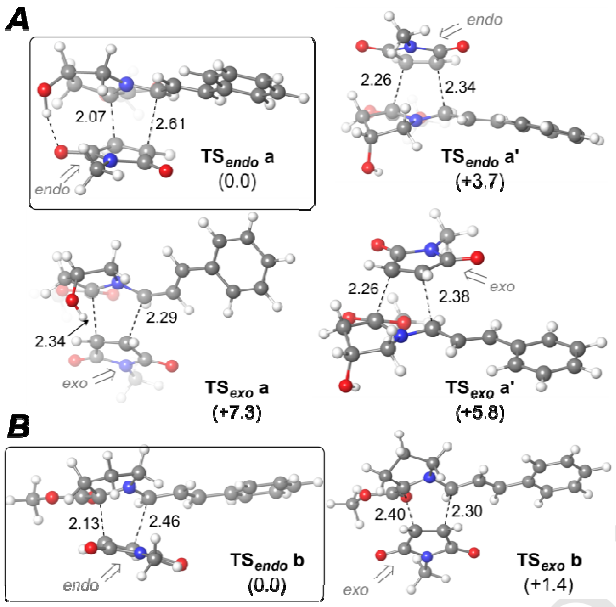


Figure 10. Main geometrical features and relative energies of the transition structures associated with the [3+2] cycloadditions of NMM with azomethine ylides (A) s-**32** or (B) and s-**33** computed at M06-2X(PCM)/def2-TZVPP//B3LYP(PCM)/6-31G* level of theory. Relative energies are given in kcal mol^{-1} and bond distances are in Å.

In the case of hydroxyproline azomethine ylide s-**32**, our calculations show that the reaction is an exothermic process with a high preference for *endo*-**19e** cycloadduct formation (Table 2, entries 1-4). The computed activation barrier associated with this product is at least ca. 4 kcal mol^{-1} lower than those associated with the formation of cycloadducts *endo*-**19e'**, *exo*-**19e** and *exo*-**19e'**. Moreover, it can be observed in Figure 10A, that the all the computed transition structures are concerted but quite asynchronous. The different distances for the two C-C bonds being formed are compatible with an α-attack of the iminium-enolate structure to NMM (Figure 3). In contrast, in the most energetic transition structure (TS$_{exo}$a) there is an inversion on the relative C-C distances, which corresponds to a γ-attack.

Our calculations indicate that *endo*-**19e** will be predominantly formed because of a favorable hydrogen bonding between the hydroxy group and the incoming dipolarophile, which is not possible in any of the other possible approaches. Moreover, a general preference of the *endo*-cycloadditions over the *exo*-approaches was observed, probably because of the presence of stabilizing coulombic and secondary orbital interactions in the former. Our computational results predict a theoretical diastereomeric ratio of 98:2:0:0 of cycloadducts *endo*-**19e**:*endo*-**19e'**:*exo*-**19e**:*exo*-**19e'**, in excellent agreement with the experimental results (Scheme 5).

Reaction of NMM with proline methyl ester derivative s-**33** was also considered. In this case, the computed activation barriers and reaction Gibbs free energies are similar to these computed for s-**32** (Table 2, entries 5-6). However, the energetic difference between the *endo*- and *exo*- approaches is lower due to less congested substitution pattern in the pyrrolidine moiety. As in the previous case, the computed transition structures were found to be concerted but asynchronous. Remarkably, in the transition structure associated with the lowest energy barrier (TS$_{endo}$b), the relative C-C distances correspond to a α-attack whereas in TS$_{exo}$b, these distances correspond to a γ-attack (Figure 10B). The computed *endo*-**23ad**:*exo*-**23ad** ratio associated with this process is 90:10, in nice agreement with the experimental results.

Reaction of cinnamaldehyde, β-nitrostyrene and 17a. The anomalous regioselectivity achieved in the reaction of cinnamaldehyde, **17a** and β-nitrostyrene as dipolarophile called our attention. The activation and reaction Gibbs free energies, as well as the main geometrical features of the transition structures were calculated and are collected in Table 3 and Figure 11, respectively.

Table 3. Computed activation and reaction Gibbs free energy on the [3+2] cycloadditions of s-**33** with β-nitrostrene computed at M06-2X(PCM)/def2-TZVPP//B3LYP(PCM)/6-31G* level of theory.

entry	ylide		cycloadduct	ΔG^a (kcal mol^{-1})	ΔG_{RXN} (kcal mol^{-1})
1	s-**33**	*endo*	*endo*-**23af**	+3.2	-23.6
2			*endo*-**24af**	+4.6	-22.3
3		*exo*	*exo*-**23af**	+8.4	-24.2
4			*exo*-**24af**	+11.0	-24.2

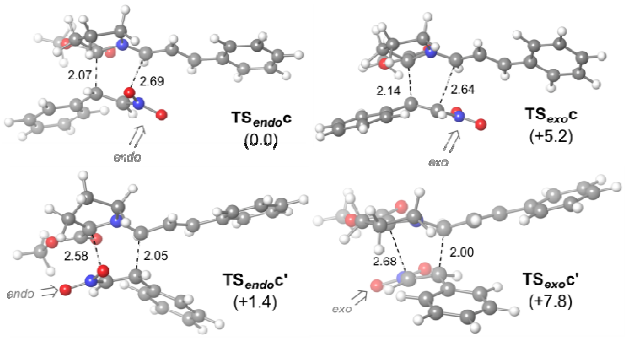


Figure 11. Main geometrical features and relative energies of the transition structures associated with all the possible [3+2] cycloadditions of s-**33** with β-nitrostrene computed at M06-2X(PCM)/def2-TZVPP//B3LYP(PCM)/6-31G* level of theory. Relative energies are given in kcal mol^{-1} and bond distances are in Å.

In this case, we observed that the formation of *endo*-**23af** had an associated activation barrier of 1.4 kcal mol^{-1} lower than that associated with the formation of its regioisomer *endo*-**24af** (Table 3). Moreover, formation of exo-analogues was kinetically disfavored. In addition, the transition structures were found to be more asynchronous than in the previous cases, in which the symmetrical NMM was used as dipolarophile. In these reactions,

higher differences between the C-C distances associated with the two new σ-bonds were obtained (Figures 10 and 11). The kinetic product distribution computed for this reaction was 90:10 for the *endo*-**23af**:*endo*-**24af** cycloadducts, associated with α- and γ-attacks, respectively, in good agreement with the experimental results.

Conclusions

In conclusion, a very efficient and mild multicomponent diastereoselective 1,3-DC of (2*S*,4*R*)-4-hydroxyproline methyl ester and other similar systems, proline and 4-thiaproline esters, aldehydes and dipolarophiles have been optimized for the final synthesis of polysubstituted pyrrolizidine alkaloids. The analysis of the general scope of the reaction allowed to direct the attack of the in situ formed 1,3-dipole. The α-attack is favored when conjugated, aromatic, and aliphatic aldehydes were used, whereas a favored γ-attack occurs with ethyl glyoxylate. In this last example the role of the silver salt was crucial, otherwise the reaction did not take place at all in its absence. With other aldehydes the presence of silver was not necessary except in the case of working with proline methyl ester and BPSE as dipolarophile and in the reactions involving crotonaldehyde and methyl acrylate. In all cases, 2,5-*trans*-relative configuration between two electron-withdrawing groups was achieved and major *endo*-selectivity (2,4-*cis*-relative configuration) was a typical feature of these transformations in the absence or in the presence of silver acetate. However, an *exo*-selectivity was mainly found when ethyl glyoxylate participated in the reaction mixture affording 2,3-*cis* and 2,5-*trans*-relative configuration. These new highly functionalized pyrrolizidines can have potential biological activity.

Computational studies show that the driving force underlying the high diastereoselection found for the [3+2] cycloadditon of hydroxyproline derivatives is a consequence of a hydrogen bonding that cannot be formed in the other approaches. In the case of proline esters, the observed lower diastereoselection is consequence to the lack of substituents on the pyrrolidine ring, being the *endo*-approach the energetically favored process. The anomalous regioselectivity found in the reaction of cinnamaldehyde, β-nitrostyrene and **17a** was found to be a consequence of a trade off between an efficient orbital overlap and the existence of different electron densities on C_α and C_γ centers. In all the cases studied, the computational results were found to be in good agreement with the experimental data.

Experimental Section

1. General.

Aldehydes were distilled prior to use for the elaboration of the iminoesters. Melting points were determined with a hot plate apparatus and are uncorrected. Only the structurally most important peaks of the IR spectra are listed. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Low-resolution electron impact (EI) mass spectra were obtained at 70eV and high-resolution mass spectra were recorded with accurate mass assignments better than 2 ppm. Microanalyses were performed selecting the appropriate standard compound. Analytical TLC was performed on silica gel plates and the spots were visualized under UV light (λ = 254 nm). For flash chromatography we employed silica gel 60 (0.040-0.063 mm). Complexes were prepared according to the reported procedure (see text). All of the transformations performed with silver catalysts were performed in the absence of light. All diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixture, and by weighting each stereoisomer after separation by flash chromatography.

Density Functional Theory[39] (DFT) geometry optimizations and harmonic analyses were performed using the hybrid B3LYP[40] functional. Relative energies were computed by means of single point calculations on the optimized geometries using the M06-2X[41] functional. This M06-2X//B3LYP hybrid theoretical level was chosen since it is known that B3LYP and M06-2X produce similar optimized geometries in this kind of reactions.[42] Moreover, the latter highly parameterized M06-2X method is well suited for the treatment of nonbonding interactions and dispersion forces.[43] The 6-31G* and def2-TZVPP basis sets were used. Solvent effects were computed by means of PCM method using toluene as solvent.[44] Reactants and products showed positive definite Hessians. Transition structures (TSs) showed one and only one imaginary frequency associated with nuclear motion along the chemical transformation under study. Free energies at 298.15 K were calculated by including the corresponding thermal corrections to Gibbs free energies (TCGE). Figures including optimized structures were made with Maestro.[45] FMO representations were prepared using Gauss-view interface.[46] Expansion coefficients were calculated using the AM1[47] semiempirical Hamiltonian.

2. General procedure for the synthesis of cycloadducts in the absence of AgOAc.

Methyl ester L-proline hydrochloride (82.8 mg, 0.5 mmol) or L-4-hydroxyproline methyl ester hydrochloride (92.1 mg, 0.5 mmol),the corresponding alkene (0.5 mmol), the aldehyde (0.5 mmol) and triethylamine (90 μL, 0.55 mmol) were dissolved in toluene (3 mL). The resulting mixture was stirred for times described across the main text. Then the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (silica gel) to afford the corresponding product.

3. General procedure for the synthesis of cycloadducts in the presence of AgOAc.

Methyl ester L-proline hydrochloride (82.8 mg, 0.5 mmol) or L-4-hydroxyproline methyl ester hydrochloride (92.1 mg, 0.5 mmol), or chiral polysubstituted prolinates (0.5 mmol)silver acetate (4.15 mg, 0.025 mmol), the corresponding alkene (0.5 mmol), the aldehyde (0.5 mmol) and triethylamine (90 μL, 0.55 mmol) were dissolved in toluene (3 mL). The resulting suspension was stirred for the corresponding time and temperature (see main text) avoiding the light exposure. Then the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (silica gel) to afford the corresponding product. Compounds 20b, *exo*-23bd, *endo*-23ae, *endo*-23ag, *endo*-25aa, and *exo*-29ab were unpurified with small unidentified substances (see spectra).

4. Physical and spectroscopic data of compounds

Dimethyl (2S,3S,6R,7aS)-6-hydroxy-3-[(E)-styryl]hexahydro-1H-pyrrolizine-2,7a-dicarboxylate ***19a***:[27] Brown needles, 117 mg (68%), mp: 99-102 ºC; $[\alpha]_D^{20}$ = +81.2 (c 1, $CHCl_3$); IR (neat) ν_{max} 3322, 2950, 2305, 1715, 1707 cm^{-1}; ^{1}H NMR δ_H: 1.97 (dd, *J* = 13.5, 4.8 Hz, 1H, C*H*HCCO$_2$Me), 2.42 (deform. dd, *J* = 12.9, 12.3 Hz, 1H, C*H*HCHCO$_2$Me), 2.54-2.61 (m, 2H, C*H*HCHCO$_2$Me, C*H*HCCO$_2$Me), 3.07-3.16 (m, 2H, CH_2N), 3.50-3.56 (m, 4H, C*H*CO$_2$Me, CHCO$_2$C*H*$_3$), 3.73 (s, 3H, CCO$_2$CH$_3$), 4.21 (dd, *J* = 10.3, 7.8 Hz, 1H, CHN), 4.56 (deform. dddd, *J* = 5.1, 5.0, 4.8, 4.7 Hz, 1H, C*H*OH), 6.23 (dd, *J* = 15.5, 10.4 Hz, 1H, C*H*CHN), 6.51 (d, *J* = 15.5 Hz, 1H, C*H*Ph), 7.23-7.38 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 36.9 (*C*H$_2$CCO$_2$Me), 45.0 (*C*H$_2$CHCO$_2$Me), 50.5 (*C*HCO$_2$Me), 51.9 (CCO$_2$*C*H$_3$), 52.7 (*C*HCO$_2$Me), 56.2 (CH$_2$N), 66.9 (CHN), 74.2 (CHOH), 75.9 (*C*CO$_2$Me), 126.7, 128.0, 128.7, 136.7 (Ar*C*), 127.5 (*C*HCHN), 136.7 (*C*HPh), 172.4 (CHCO$_2$Me), 176.5 (C*C*O$_2$Me); MS (EI-GC) *m/z*: 345 (M$^+$, <1%), 269 (11), 268 (100), 243 (11), 241 (15), 209 (15), 126 (11), 105 (13); Microanalysis calculated for $C_{19}H_{23}NO_5$: C, 66.1; H, 6.7; N, 4.1%; found: C, 66.5; H, 7.0; N, 4.3%.

Dimethyl (2R,3R,6R,7aR)-6-hydroxy-3-[(E)-styryl]hexahydro-1H-pyrrolizine-2,7a-dicarboxylate ***19a'***:[27] Brown needles, 29 mg (17%), mp: 95-97 ºC; $[\alpha]_D^{20}$ = +34.7 (c 1, $CHCl_3$); IR (neat) ν_{max} 3396, 2944, 2315, 1717, 1698 cm^{-1}; ^{1}H NMR δ_H: 2.06 (dd, *J* = 14.0, 6.1 Hz, 1H, C*H*HCCO$_2$Me), 2.24 (dd,

J = 13.4, 11.7 Hz, 1H, C*H*HCHCO$_2$Me), 2.50 (dd, *J* = 14.0, 1.8 Hz, 1H, C*H*HCCO$_2$Me), 2.63 (dd, *J* = 13.4, 7.0 Hz, 1H, C*H*HCHCO$_2$Me), 2.92 (dd, *J* = 11.7, 2.5 Hz, 1H, C*H*HN), 3.50-3.53 (m, 4H, C*H*CO$_2$Me, CHCO$_2$C*H*$_3$), 3.76 (s, 3H, CCO$_2$CH$_3$), 4.16 (dd, *J* = 10.4, 7.4 Hz, 1H, CHN), 4.44 (m, 1H, C*H*OH), 5.87 (dd, *J* = 15.6, 10.4 Hz, 1H, C*H*CHN), 6.57 (d, *J* = 15.5 Hz, 1H, C*H*Ph), 7.27-7.31 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 36.9 (CH$_2$CCO$_2$Me), 46.5 (CH$_2$CHCO$_2$Me), 50.7 (CHCO$_2$Me), 52.0 (CCO$_2$CH$_3$), 53.0 (CHCO$_2$Me), 57.0 (CH$_2$N), 66.5 (CHN), 75.0 (CHOH), 75.5 (CCO$_2$Me), 125.3 (CHCHN), 126.7, 128.2, 128.8, 136.3 (Ar*C*), 136.0 (CHPh), 172.3 (CHCO$_2$Me), 177.3 (CCO$_2$Me); MS (EI-GC) *m/z*: 345 (M$^+$, <1%), 269 (13), 268 (100), 243 (10), 241 (31), 209 (22), 105 (11), 59 (10); Microanalysis calculated for $C_{19}H_{23}NO_5$: C, 66.1; H, 6.7; N, 4.1%; found: C, 66.4; H, 6.9; N, 4.1%.

Dimethyl (2S,3S,6R,7aS)-6-[(tert-butyldimethylsilyl)oxy]-3-[(E)-styryl]hexahydro-1H-pyrrolizine-2,7a-dicarboxylate ***19b***:[27] Sticky orange oil, 143 mg (62%); $[\alpha]_D^{20}$= +4.2 (c 1, CHCl$_3$); IR (neat) ν_{max} 3396, 2944, 2315, 1717, 1698 cm^{-1}; ^{1}H NMR δ_H: -0.04 (s, 6H, OTBS), 0.81 (s, 9H, OTBS), 1.95 (dd, *J* = 13.0, 6.0 Hz, 1H, C*H*HCCO$_2$Me), 2.28 (deform. dd, *J* = 13.2, 13.0 Hz, 1H, C*H*HCHCO$_2$Me), 2.40-2.51 (m, 2H, C*H*HCHCO$_2$Me, C*H*HCCO$_2$Me), 2.8 (dd, *J* = 11.6, 4.7 Hz, 1H, C*H*HN), 3.20 (dd, *J* = 11.6, 5.4 Hz, 1H, C*H*HN), 3.49-3.56 (m, 4H, C*H*CO$_2$Me, CHCO$_2$C*H*$_3$), 3.74 (s, 3H, CCO$_2$CH$_3$), 4.18 (dd, *J* = 10.5, 7.2 Hz, 1H, CHN), 4.56 (deform. dddd, *J* = 6.0, 5.4, 5.3, 4.7 Hz, 1H, C*H*OH), 5.85 (dd, *J* = 15.6, 10.5 Hz, 1H, C*H*CHN), 6.54 (d, *J* = 15.6 Hz, 1H, C*H*Ph), 7.24-7.30 (m, 5H, Ar*H*); ^{13}C NMR δ_C: -4.8, -4.9 (OTBS), 18.2 (OTBS), 25.9 (OTBS), 37.5 (CH$_2$CCO$_2$Me), 46.4 (CH$_2$CHCO$_2$Me), 49.4 (CHCO$_2$Me), 51.9 (CCO$_2$CH$_3$), 52.7 (CHCO$_2$Me), 56.3 (CH$_2$N), 66.9 (CHN), 74.5 (CHOH), 74.7 (CCO$_2$Me), 125.4 (CHCHN), 126.7, 128.2, 128.7, 136.4 (Ar*C*), 136.0 (CHPh), 171.9 (CHCO$_2$Me), 176.9 (CCO$_2$Me); MS (EI-GC) *m/z*: 459 (M$^+$, <1%), 327 (10), 268 (100), 267 (11), 243 (15), 242 (10), 241 (21), 209 (17), 208 (10), 106 (10), 105 (10); HRMS calculated for $C_{25}H_{37}NO_5Si$ +1: 460.2519; found: 460.2522.

Endo-19b' could not be separated.

2-tert-Butyl 7a-methyl (2S,3S,6R,7aS)-6-hydroxy-3-[(E)-styryl]hexahydro-1H-pyrrolizine-2,7a-dicarboxylate ***19c***:[27] Sticky yellow oil, 112 mg (81%); $[\alpha]_D^{20}$= -124.7 (c 1, CHCl$_3$); IR (neat) ν_{max} 2985, 2939, 2305, 1714, 1691 cm^{-1}; ^{1}H NMR δ_H: 1.26 [s, 9H, CO$_2$C(C*H*$_3$)$_3$], 1.94 (dd, *J* = 13.4, 5.1 Hz, 1H, C*H*HCCO$_2$Me), 2.37 (deform. dd, *J* = 12.6, 12.3 Hz, 1H, C*H*HCHCO$_2$Bu^t), 2.50-2.59 (m, 2H, C*H*HCHCO$_2$Bu^t, C*H*HCCO$_2$Me), 3.08-3.15 (m, 2H, CH$_2$N), 3.44 (ddd, *J* = 12.3, 7.5, 6.7 Hz, 1H, CHCO$_2$Bu^t), 3.72 (s, 3H, CCO$_2$C*H*$_3$), 4.16 (dd, *J* = 10.4, 7.5 Hz, 1H, CHN), 4.54 (deform. dddd, *J* = 5.5, 5.3, 5.1, 4.9 Hz, 1H, C*H*OH), 6.24 (dd, *J* = 15.6, 10.4 Hz, 1H, C*H*CHN), 6.51 (d, *J* = 15.6 Hz, 1H, C*H*Ph), 7.20-7.38 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 28.2 [CO$_2$C(C*H*$_3$)$_3$], 36.9 (CH$_2$CCO$_2$Me), 45.2 (CH$_2$CHCO$_2$Bu^t), 51.2 (CCO$_2$CH$_3$), 52.6 (CHCO$_2$Bu^t), 56.0 (CH$_2$N), 66.9 (CHN), 74.3 (CHOH), 75.7 (CCO$_2$Me), 80.9 [CO$_2$C(CH$_3$)$_3$], 126.7, 127.9, 128.7, 136.6 (Ar*C*), 127.7 (CHCHN), 134.9 (CHPh), 171.1 (CHCO$_2$Bu^t), 176.7 (CCO$_2$Me); MS (EI-GC) *m/z*: 387 (M$^+$, <1%), 369 (11), 329 (10), 310 (15), 268 (30), 209 (100), 241 (11), 240 (17), 105 (12);Microanalysis calculated for $C_{22}H_{29}NO_5$: C, 68.2; H, 7.5; N, 3.6%; found: C, 68.5; H, 7.3; N, 3.7%.

2-tert-Butyl 7a-methyl (2R,3R,6R,7aR)-6-hydroxy-3-[(E)-styryl]hexahydro-1H-pyrrolizine-2,7a-dicarboxylate ***19c´***:[27] Sticky brown oil, 11 mg (8%); $[\alpha]_D^{20}$= +43.3 (c 1, CHCl$_3$); IR (neat) ν_{max} 3002, 2955, 2315, 1721, 1708 cm^{-1}; ^{1}H NMR δ_H: 1.30 [s, 1H, CO$_2$C(C*H*$_3$)$_3$], 2.03 (dd, *J* = 13.9, 6.1 Hz, 1H, C*H*HCCO$_2$Me), 2.16 (dd, *J* = 13.4, 11.9 Hz, 1H, C*H*HCHCO$_2$Bu^t), 2.49 (dd, *J* = 14.0, 2.0 Hz, 1H, C*H*HCCO$_2$Me), 2.58 (dd, *J* = 13.4, 6.9 Hz, 1H, C*H*HCHCO$_2$Bu^t), 2.91 (dd, *J* = 11.7, 2.5 Hz, 1H, C*H*HN), 3.37 (dd, *J* = 11.7, 5.4 Hz, 1H, C*H*HN), 3.49 (dd, *J* = 11.9, 7.4 Hz, 1H, CHCO$_2$Bu^t), 3.78 (s, 3H, CCO$_2$CH$_3$), 4.11 (dd, *J* = 10.4, 7.4 Hz, 1H, CHN), 4.40 (m, 1H, C*H*OH), 5.88 (dd, *J* = 15.6, 10.4 Hz, 1H, C*H*CHN), 6.57 (d, *J* = 15.5 Hz, 1H, C*H*Ph), 7.26-7.37 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 28.2 [CO$_2$C(C*H*$_3$)$_3$], 36.8 (CH$_2$CCO$_2$Me), 46.5 (CH$_2$CHCO$_2$Bu^t), 51.4 (CCO$_2$CH$_3$), 53.0 (CHCO$_2$Bu^t), 57.1 (CH$_2$N), 66.6 (CHN), 75.2 (CHOH), 75.5 (CCO$_2$Me), 81.1 [CO$_2$C(CH$_3$)$_3$], 125.7 (CHCHN), 126.7, 128.2, 128.8, 136.0 (Ar*C*), 136.3 (CHPh), 171.0 (CHCO$_2$Bu^t), 176.5 (CCO$_2$Me); MS (EI-GC) *m/z*: 387 (M$^+$, <1%), 369 (10), 329 (10), 328 (11), 311 (15), 310 (13), 209 (100), 241 (13), 240 (21), 105 (10); Microanalysis calculated for $C_{22}H_{29}NO_5$: C, 68.2; H, 7.5; N, 3.6%; found: C, 68.6; H, 7.4; N, 3.5%.

Methyl (1S,2S,3S,6R,7aR)-6-hydroxy-1-methyl-2-(2-oxooxazolidine-3-carbonyl)-3-[(E)-styryl]hexahydro-1H-pyrrolizine-7a-carboxylate ***19d***: Yellow needles, 161 mg (78%), mp: 122-124 ºC; $[\alpha]_D^{20}$= -199.9 (c 1, CHCl$_3$); IR (neat) ν_{max} 2948, 2923, 2874, 1776, 1725, 1690, 1387, 1213 cm^{-1}; ^{1}H NMR δ_H: 0.96 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.83 (br. s, 1H, OH), 1.92 (dd, *J* = 13.7, 4.7 Hz, 1H, C*H*HC(CO$_2$Me)], 2.77 [dd, *J* = 13.7, 6.0 Hz, 1H, C*H*HC(CO$_2$Me)], 2.98-3.16 (m, 3H, C*H*$_2$N, C*H*CH$_3$), 3.67 (ddd, *J* = 10.9, 9.3, 6.6 Hz, 1H, C*H*HNCO), 3.76 (s, 3H, CO$_2$C*H*$_3$), 3.93 (ddd, *J* = 10.9, 9.4, 7.0 Hz, 1H, C*H*HNCO), 4.12 (deform ddd, *J* = 9.4, 9.2, 7.0 Hz, 1H, C*H*HOCO), 4.28 (deform ddd, *J* = 9.3, 9.2, 6.6 Hz, 1H, C*H*HOCO), 4.44 (m, 1H, C*H*OH), 4.53 (dd, *J* = 11.4, 8.5 Hz, 1H, C*H*CON), 4.59 (dd, *J* = 10.2, 8.5 Hz, 1H, C*H*N), 6.27 (dd, *J* = 15.7, 10.2 Hz, 1H, C*H*CHN), 6.51 (d, *J* = 15.7 Hz, 1H, C*H*Ph), 7.20-7.36 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 13.4 (CHCH$_3$), 42.8 (CH$_2$CCO$_2$Me), 43.0 (CH$_2$N), 44.1 (CHCH$_3$), 52.2 (CHCON), 56.1 (CH$_2$NCO), 56.3 (CO$_2$CH$_3$), 62.2 (CH$_2$OCO), 64.7 (CHN), 73.5 (CHOH), 79.3 (CCO$_2$Me), 126.7, 128.1, 128.8, 136.5 (Ar*C*), 128.1 (CHCHN), 134.1 (CHPh), 153.0 (NCO$_2$), 171.4 (CON), 175.4 (CCO$_2$Me); MS (EI-GC) *m/z*: 414 (M$^+$, <1%), 259 (16), 231 (10), 201 (15), 200 (100), 182 (35), 172 (20), 156 (10), 115 (25); HRMS calculated for $C_{22}H_{26}N_2O_6$ +1: 415.1869; found: 415.1852.

Methyl (1R,2R,3R,6R,7aS)-6-hydroxy-1-methyl-2-(2-oxooxazolidine-3-carbonyl)-3-[(E)-styryl]hexahydro-1H-pyrrolizine-7a-carboxylate ***19d´***: Yellow needles, 9 mg (4%),mp: 106-109 ºC; $[\alpha]_D^{20}$= +112.9 (c 1, CHCl$_3$); IR (neat) ν_{max} 2949, 2921, 1776, 1728, 1688, 1387, 1217 cm^{-1}; ^{1}H NMR δ_H: 0.99 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 2.00 (dd, *J* = 13.7, 5.3 Hz, 1H, C*H*HC(CO$_2$Me)], 2.69-2.79 [m, 2H, C*H*CH$_3$, C*H*HC(CO$_2$Me)], 2.87 (ddd, *J* = 11.0, 2.4, 1.0 Hz, 1H, C*H*HN), 3.25 (dd, *J* = 11.0, 4.5 Hz, 1H, C*H*HN), 3.72 (ddd, *J* = 10.9, 9.3, 6.7 Hz, 1H, C*H*HNCO), 3.79 (s, 3H, CO$_2$C*H*$_3$), 3.94 (ddd, *J* = 10.9, 9.4, 6.9 Hz, 1H, C*H*HNCO), 4.14 (deform ddd, *J* = 9.3, 9.1, 6.9 Hz, 1H, C*H*HOCO), 4.30 (deform ddd, *J* = 9.4, 9.1, 6.7 Hz, 1H, C*H*HOCO), 4.44 (m, 1H, C*H*OH), 4.55 (dd, *J* = 11.2, 8.3 Hz, 1H, C*H*CON), 4.63 (dd, *J* = 10.4, 8.3 Hz, 1H, C*H*N), 5.98 (dd, *J* = 15.5, 10.4 Hz, 1H, C*H*CHN), 6.56 (d, *J* = 15.5 Hz, 1H, C*H*Ph), 7.22-7.37 (m, 5H, Ar*H*), OH nd; ^{13}C NMR δ_C: 13.6 (CHCH$_3$), 42.8 (CH$_2$CCO$_2$Me), 44.1 (CHCH$_3$), 44.3 (CH$_2$N), 52.4 (CHCON), 56.5 (CH$_2$NCO), 56.8 (CO$_2$CH$_3$), 62.2 (CH$_2$OCO), 64.1 (CHN), 74.2 (CHOH), 78.6 (CCO$_2$Me), 126.7, 128.3, 128.9, 136.3 (Ar*C*), 126.8 (CHCHN), 135.2 (CHPh), 153.0 (NCO$_2$), 171.5 (CON), 175.5 (CCO$_2$Me); MS (EI-GC) *m/z*: 414 (M$^+$, <1%), 259 (18), 231 (11), 201 (11), 200 (100), 183 (10), 182 (35), 172 (27), 115 (19); HRMS calculated for $C_{22}H_{26}N_2O_6$ +1: 415.1869; found: 415.1860.

Methyl (3aS,4S,7R,8aR,8bR)-7-hydroxy-2-methyl-1,3-dioxo-4-[(E)-styryl]decahydropyrrolo[3,4-a]pyrrolizine-8a-carboxylate ***19e***:[27] Sticky yellow oil, 112 mg (61%); $[\alpha]_D^{20}$= +78.1 (c 1, CHCl$_3$); IR (neat) ν_{max} 3005, 2980, 2305, 1714, 1710, 1698 cm^{-1}; ^{1}H NMR δ_H: 2.31-2.41 (m, 1H, C*H*HCCO$_2$Me), 2.71-2.83 (m, 3H, C*H*HCCO$_2$Me, CH$_2$N), 2.97 (s, 3H, NCH$_3$), 3.52 (deform. dd, *J* = 8.5, 8.1 Hz, 1H, C*H*CON), 3.85 (s, 3H, CO$_2$CH$_3$), 3.95 (d, *J* = 8.1 Hz, 1H, CHCCO$_2$Me), 4.21 (deform. dd, *J* = 9.1, 8.5 Hz, 1H, C*H*N), 4.36 (m, 1H, CHOH), 6.23 (dd, *J* = 15.6, 9.1 Hz, 1H, C*H*CHN), 6.76 (d, *J* = 15.6 Hz, 1H, C*H*Ph), 7.26-7.40 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 26.1 (NCH$_3$), 37.3 (CH$_2$CCO$_2$Me), 52.3, 53.1, (2xCHCON), 54.4 (CCO$_2$CH$_3$), 55.1 (CH$_2$N), 65.7 (CHN), 75.3 (CHOH), 77.9 (CCO$_2$CH$_3$), 125.3 (CHCHN), 126.9, 128.2, 128.7, 135.7 (Ar*C*), 136.0 (CHPh), 176.2, 176.3 (2xCON), 177.1 (CO$_2$Me); MS (EI-GC) *m/z*: 370 (M$^+$, <1%), 352 (10), 312 (10), 293 (100), 243 (21), 210 (12), 182 (40), 115 (10); HRMS calculated for $C_{20}H_{22}N_2O_5$ +1: 371.1607; found: 371.1621.

*Endo-**19e'** could not be separated.*

2-tert-Butyl 7a-methyl (2S,3R,6R,7aS)-6-hydroxy-3-phenylhexahydro-1H-pyrrolizine-2,7a-dicarboxylate ***20a***: Colorless prisms, 98 mg (75%), mp: 108-112 ºC; $[\alpha]_D^{20}$= -2.4 (c 1, CHCl$_3$); IR (neat) ν_{max} 3196, 2977, 2954, 2899, 1719, 1162 cm^{-1}; ^{1}H NMR δ_H: 1.26 [s, 9H, CO$_2$C(C*H*$_3$)$_3$], 1.80 (m, 1H, OH), 1.84 (dd, *J* = 12.5, 8.5 Hz, 1H, C*H*HCHCO$_2$Bu^t), 2.40-2.55 (m, 3H, C*H*HN, C*H*HCCO$_2$Me, C*H*HCHCO$_2$Bu^t), 2.71 (dd, *J* = 12.4, 6.4 Hz, 1H, C*H*HCCO$_2$Me), 2.94 (dd, *J* = 9.5, 6.5 Hz, 1H, C*H*HN), 3.74 (s, 3H, CCO$_2$C*H*$_3$), 3.80 (ddd, *J* = 12.5, 9.0, 7.7 Hz, 1H, C*H*CO$_2$Bu^t), 4.64 (d, *J* = 9.0 Hz, 1H, C*H*N), 4.65 (deform. dddd, *J* = 6.5, 6.5, 4.6, 4.5 Hz, 1H, C*H*OH), 7.22-7.33 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 27.5 [CO$_2$C(C*H*$_3$)$_3$], 37.4 (CH$_2$CCO$_2$Me), 44.7 (CH$_2$CHCO$_2$Bu^t), 52.5 (CCO$_2$CH$_3$), 55.7 (CHCO$_2$Bu^t), 54.3 (CH$_2$N), 66.7 (CHN), 74.9 (CHOH), 77.2 (CCO$_2$Me), 80.6

$[CO_2C(CH_3)_3]$, 128.0, 128.4, 129.8, 138.2 (Ar*C*), 170.8 ($CHCO_2Bu^t$), 176.6 (CCO_2Me); MS (EI-GC) *m/z*: 361 (M^+, <1%), 303 (11), 302 (51), 247 (17), 246 (100); HRMS calculated for $C_{20}H_{27}NO_5$+1: 362.1967; found: 369.1970.

Methyl (1R,2R,3S,6R,7aS)-6-hydroxy-3-phenyl-1,2-bis(phenylsulfonyl)hexahydro-1H-pyrrolizine-7a-carboxylate ***20b***: Yellow solid, 146 mg (54%), mp: 73-75 ºC; $[\alpha]_D^{20}$= +21.5 (c 1, $CHCl_3$); IR (neat) ν_{max} 2975, 1715, 1300, 1151 cm^{-1}; ^1H NMR δ_H: 2.08 (dd, *J* = 14.4, 0.5 Hz, 1H, C*H*HN), 2.59 (dd, , *J* = 9.4, 2.4 Hz, 1H, C*H*HCCO$_2$Me), 3.17 (dd, , *J* = 9.4, 5.5 Hz, 1H, C*H*HCCO$_2$Me), 2.08 (dd, *J* = 14.4, 6.6 Hz, 1H, C*H*HN), 3.90 (s, 3H, CO_2CH_3), 4.27 (dd, *J* = 6.8, 4.2 Hz, 1H, C*H*SO$_2$Ph), 4.53 (m, 1H, C*H*OH), 4.62 (d, *J* = 6.8 Hz, 1H, C*H*SO$_2$Ph), 4.86 (d, *J* = 4.2 Hz, 1H, C*H*Ph), 7.11-7.98 (m, 15H, Ar*H*); ^{13}C NMR δ_C: 41.6 (CH_2CCO_2Me), 53.3 (CO_2CH_3), 54.1 (CH_2N), 62.9, 65.9 [2x*C*H(SO$_2$Ph)], 73.4 (CHN), 73.8 (CHOH), 77.5 (CCO_2Me), 128.3 128.5, 129.0, 129.5, 129.6, 129.9, 134.1, 134.5, 136.6, 137.2, 138.1, 140.3 (Ar*C*), 136.0 (*C*HPh), 174.1 (CCO_2Me); MS (EI-GC) *m/z*: 541 (M^+, <1%), 251 (11), 250 (76), 184 (11), 141 (41), 125 (100), 110 (10), 109 (47), 78 (10), 77 (80), 65 (21), 51 (22); HRMS calculated for $C_{27}H_{27}NO_7S_2$ +1: 542.1307; found: 542.1310.

Methyl (2S,4R)-1-[2-(tert-butoxycarbonyl)propyl]-4-hydroxypyrrolidine-2-carboxylate ***21***: Sticky yellow oil, 72 mg (84%); $[\alpha]_D^{20}$= +61.5 (c 1, $CHCl_3$); IR (neat) ν_{max} 3192, 2971, 1718, 1689 cm^{-1}; ^1H NMR δ_H: 1.44 [s, 9H, $CO_2C(CH_3)_3$], 1.26 [s, 9H, $CO_2C(CH_3)_3$], 2.04-2.10 (m, 1H, C*H*HCO$_2$Bu^t), 2.20-2.26 (m, 1H, C*H*HCO$_2$Bu^t), 2.43 (deform. dd, *J* = 7.6, 7.4 Hz, 2H, C*H*CO$_2$Me), C*H*$_2$(CHNCO$_2$Me)], 2.57 [dd, *J* = 10.1, 3.3 Hz, 1H, C*H*H(NCH$_2$OH)], 2.83 [deform. ddd, *J* = 12.4, 7.6, 7.4 Hz, 1H, C*H*H(NCH$_2$)], 3.01 [deform. ddd, *J* = 12.4, 7.6, 7.5 Hz, 1H, C*H*H(NCH$_2$)], 3.38 [dd, *J* = 10.1, 5.5 Hz, 1H, C*H*H(NCH$_2$OH)], 3.63 (deform. dd, *J* = 7.6, 7.4 Hz, 1H, C*H*CO$_2$Me), 3.72 (s, 3H, CO_2CH_3), 4.46 (deform. dddd, *J* = 6.5, 6.5, 3.5, 3.3 Hz, 1H, C*H*OH); ^{13}C NMR δ_C: 28.2 [$CO_2C(CH_3)_3$], 34.8 ($CH_2CO_2Bu^t$), 39.6 (CH_2(CHNCO$_2$Me), 49.2 (CH_2N), 52.0 (CO_2CH_3), 61.0 (CH_2(NCH$_2$OH), 63.8 (*C*HNCO$_2$Me), 70.5 (CHOH), 80.7 [$CO_2C(CH_3)_3$], 171.7 (CO_2Bu^t), 174.0 (CO_2Me); MS (EI-GC) *m/z*: 259 (M^+, <1%), 243 (10), 242 (11), 200 (17), 158 (23), 144 (100); HRMS calculated for $C_{12}H_{21}NO_5$ +1: 260.1498; found: 260.1509.

Methyl (3aR,3bR*,3cR*,6aS*,7S*,9R*,9aS*)-2-methyl-1,3,4,6-tetraoxo-5,9-diphenyl-7-[(E)-styryl]dodecahydro-3bH-dipyrrolo[3,4-a:3',4'-f]pyrrolizine-3b-carboxylate endo-* ***22a***: Pale yellow oil, 27 mg (67%); IR (neat) ν_{max} 1725-1700, 1300, 1151 cm^{-1}; 1H NMR δ_H: 1.22 (dd, J = 6.5, 1.7 Hz), 2.77 (s, 3H, NC*H*$_3$), 3.47 (m, 1H, =CCHC*H*), 3.50 (dd, J = 10.4, 8.2 Hz, PhCHC*H*), 3.93 (s, 3H, CO_2CH_3), 4.24 (dd. *J* = 9.3, 9.3 Hz, 1H, NC*H*C=), 4.30 (d, *J* = 8.2 Hz, 1H, CC*H*CONPh), 4.47 (d, *J* = 10.4 Hz, 1H, CC*H*CONMe), 4.53 (d, *J* = 8.3 Hz, 1H, NC*H*Ph), 5.16 (ddd, *J* = 14.9, 9.9, 1.7 Hz, 1H, CH$_3$CH=C*H*), 5.55 (ddd, *J* = 14.9, 6.5, 0.6 Hz, 1H, CH$_3$C*H*=) 7.15-7.25 (m, 5H, Ar*H*), 7.31 (dd, *J* = 8.5, 1.3 Hz, 2H, Ar*H*), 7.49 (d, *J* = 7.4 Hz, 1H, Ar*H*), 7.57 (dd, *J* = 7.5, 1.0 Hz, 2H, Ar*H*) ^{13}C NMR δ_C: 17.2 (=C*C*H$_3$), 24.9 (NCH$_3$), 48.4 (MeNC*C*HCH), 49.9 (MeNC*C*HC), 50.3 (CHCHCHC=), 52.4 (CHCHCHC=), 53.5 (CO_2CH_3) , 66.1 (NCHCH=), 66.7 (NCHPh), 80.9 (NCCO$_2$Me), 123.2, 125.6, 127.2, 128.1, 128.2, 129.1, 129.6, 131.5, 133.6, 138.7 (Ar*C*), 170.5, 173.5, 174.6, 174.9, 175.9 (4 x N*C*=O, *C*O$_2$Me). MS (EI-GC) *m/z*: 575 (M^+, <1%), 513(8), 455(25), 454(83), 341(21), 340(100), 193(100), 282(14), 281(66); HRMS calculated for $C_{34}H_{29}N_3O_6$: 575.2159; found: 575.2155.

Dimethyl (2S,3S*,7aR*)-3-[(E)-styryl]hexahydro-1H-pyrrolizine-2,7a-dicarboxylate* ***23aa***:[27] Pale orange needles, 132 mg (80%), mp: 107-110 ºC; IR (neat) ν_{max} 2985, 2939, 2305, 1714, 1691 cm^{-1}; ^1H NMR δ_H: 1.72–1.93 (m, 3H, C*H*$_2$CH$_2$N, C*H*HCCO$_2$Me), 2.22 (deform. dd, *J* = 13.0, 12.8 Hz, 1H, C*H*HCHCO$_2$Me), 2.31 (deform. ddd, *J* = 8.6, 6.9 Hz, 1H, C*H*HCCO$_2$Me), 2.64 (dd, *J* = 13.0, 6.7 Hz, 1H, C*H*HCHCO$_2$Me), 2.89 (deform. ddd, *J* = 11.2, 6.7, 2.3 Hz, 1H, C*H*HN), 3.10 (m, 1H, C*H*HN), 3.51-3.58 (m, 4H, CHCO$_2$Me, CHCO$_2$C*H*$_3$), 3.75 (s, 3H, CCO_2CH_3), 4.19 (dd, *J* = 10.4, 6.4 Hz, 1H, CHN), 5.98 (dd, *J* = 15.5, 10.4 Hz, 1H, C*H*CHN), 6.56 (d, *J* = 15.5 Hz, 1H, C*H*Ph), 7.28-7.35 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 28.0 (CH_2CH_2N), 36.5 (CH_2CCO_2Me), 37.2 (CH_2CHCO_2Me), 48.8 (CH_2N), 50.0 ($CHCO_2Me$), 51.9 ($CHCO_2CH_3$), 52.6 (CCO_2CH_3), 67.4 (CHN), 76.4 (CCO_2Me), 125.7 (*C*HCHN), 126.7, 128.0, 128.7, 136.5 (Ar*C*), 135.5 (*C*HPh), 172.2 (CHCO$_2$Me), 177.0 (CCO$_2$Me); MS (EI-GC) *m/z*: 329 (M^+, 3%), 271 (19), 270 (100), 243 (13), 238 (21), 210 (17), 184 (40), 123 (10), 115 (10); Microanalysis calculated for $C_{19}H_{23}NO_4$: C, 69.3; H, 7.0; N, 4.3%; found: C, 69.5; H, 7.2; N, 4.5%.

7a-Benzyl 2-methyl (2S,3S*,7aR*)-3-[(E)-styryl]hexahydro-1H-pyrrolizine-2,7a-dicarboxylate* ***23ba***: Brown prisms, 188 mg, (93%), mp: 100-103 ºC; IR (neat) ν_{max} 2985, 2310, 1717 cm^{-1}; ^1H NMR δ_H: 1.72–1.81, 1.84-1.97 (m, 3H, C*H*$_2$CH$_2$N, C*H*HCCO$_2$Me), 2.24 (deform. dd, *J* = 13.3, 12.3 Hz, 1H, C*H*HCHCO$_2$Me), 2.32 (deform. ddd, *J* = 11.9, 8.6, 2.0 Hz, 1H, C*H*HCCO$_2$Me), 2.66 (dd, *J* = 13.3, 6.7 Hz, 1H, C*H*HCHCO$_2$Me), 2.93 (deform. ddd, *J* = 11.1, 6.8, 2.4 Hz, 1H, C*H*HN), 3.11 (deform. ddd, *J* = 8.8, 6.8, 5.0 Hz, 1H, C*H*HN), 3.49-3.58 (m, 4H, CHCO$_2$Me, CHCO$_2$C*H*$_3$), 4.22 (dd, *J* = 10.4, 7.5 Hz, 1H, CHN), 5.18 (d, *J* = 12.4 Hz, 1H, C*H*HPh), 5.23 (d, *J* = 12.4 Hz, 1H, C*H*HPh), 5.99 (dd, *J* = 15.5, 10.4 Hz, 1H, C*H*CHN), 6.58 (d, *J* = 15.5 Hz, 1H, C*H*Ph), 7.22-7.39 (m, 10H, Ar*H*); ^{13}C NMR δ_C: 28.0 (CH_2CH_2N), 36.4 (CH_2CCO_2Me), 37.2 (CH_2CHCO_2Me), 48.8 (CH_2N), 50.0 ($CHCO_2Me$), 51.9 ($CHCO_2CH_3$), 66.9 (CH_2Ph), 67.4 (CHN), 76.5 (CCO_2Me), 125.8 (*C*HCHN), 126.7, 127.1, 128.1, 128.3, 128.7, 128.8, 136.2, 136.6 (Ar*C*), 135.5 (*C*HPh), 172.2 (CHCO$_2$Me), 176.1 (CCO$_2$Bn); MS (EI-GC) *m/z*: 405 (M^+, <1%), 185 (14), 184 (100), 156 (10); HRMS calculated for $C_{25}H_{27}NO_4$ +1:406.2018; found: 406.2014.

2-Allyl 7a-methyl (2S,3S*,7aR*)-2-methyl-3-[(E)-styryl]hexahydro-1H-pyrrolizine-2,7a-dicarboxylate* ***23ab***:[27] Brown-yellow solid, 151 mg (82%), mp: 90-95 ºC; IR (neat) ν_{max} 2983, 1720, 1699, 2310, 1270 cm^{-1}; ^1H NMR δ_H: 1.44 (s, 3H, CCH$_3$), 1.69-2.02 (m, 3H, C*H*$_2$CH$_2$N, C*H*HCCO$_2$Me), 2.15-2.24 (m, 1H, C*H*HCCO$_2$Me), 2.51 [d, *J* = 13.7 Hz, 1H, C*H*HC(CH$_3$)CO$_2$Allyl], 2.64 [d, *J* = 13.7 Hz, 1H, C*H*HC(CH$_3$)CO$_2$Allyl], 2.92-3.01 (m, 1H, C*H*HN), 3.08-3.16 (m, 1H, C*H*HN), 3.77 (s, 3H, CCO_2CH_3), 3.80 (d, *J* = 10.4, Hz, 1H, CHN), 4.43-4.45 (m, 2H, $CO_2CH_2CHCH_2$), 5.07 (ddd, *J* = 10.4, 2.6, 1.2 Hz, 1H, CO_2CH_2CHCHH), 5.19 (ddd, *J* = 17.2, 2.6, 1.2 Hz, 1H, CO_2CH_2CHCHH), 5.75 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H, $CO_2CH_2CHCH_2$), 5.95 (dd, *J* = 15.6, 10.4 Hz, 1H, C*H*CHN), 6.53 (d, *J* = 15.6 Hz, 1H, C*H*Ph), 7.23-7.34 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 23.5 (CCH$_3$), 27.5 (CH_2CH_2N), 39.2 (CH_2CCO_2Me), 43.9 [$CH_2C(CH_3)CO_2Allyl$], 49.0 (CH_2N), 52.7 (CCO_2CH_3), 55.5 (CCO_2CH_3), 65.7 ($CO_2CH_2CHCH_2$), 74.6 (CHN), 77.4 [*C*(CH$_3$)CO$_2$Allyl], 118.6 ($CO_2CH_2CHCH_2$), 126.1 (*C*HCHN), 126.7, 127.9, 128.7, 136.6 (Ar*C*), 132.1 ($CO_2CH_2CHCH_2$), 135.4 (*C*HPh), 174.4 (CO_2Allyl), 178.0 (CO_2Me); MS (EI-GC) *m/z*: 369 (M^+, <1%), 310 (33), 243 (34), 185 (15), 184 (100), 115 (11); Microanalysis calculated for $C_{22}H_{27}NO_4$: C, 71.5; H, 7.4; N, 3.8%; found: C, 72.2; H, 7.1; N, 4.2%.

Methyl (1S,2S*,3S*,7aR*)-1-methyl-2-(2-oxooxazolidine-3-carbonyl)-3-[(E)-styryl]hexahydro-1H-pyrrolizine-7a-carboxylate* ***23ac***: Yellowish needles, 159 mg (80%), mp: 115-118 ºC; IR (neat) ν_{max} 2975, 2959, 2927, 2912, 1775, 1716, 1688, 1388, 1265 cm^{-1}; ^1H NMR δ_H: 0.98 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.69-1.86 [m, 3H, C*H*$_2$CH$_2$N, C*H*HC(CO$_2$Me)], 2.52 [deform ddd, *J* = 10.8, 6.9, 6.8 Hz, 1H, C*H*HC(CO$_2$Me)], 2.72 (dq, *J* = 11.6, 6.8 Hz, 1H, C*H*CH$_3$), 2.80 (deform ddd, *J* = 11.9, 10.8, 6.0 Hz, 1H, C*H*HN), 3.08 (deform ddd, *J* = 11.9, 10.6, 6.4 Hz, 1H, C*H*HN), 3.70 (ddd, *J* = 10.9, 9.3, 6.6 Hz, 1H, C*H*HNCO), 3.77 (s, 3H, CO_2CH_3), 3.94 (ddd, *J* = 10.9, 9.4, 6.9 Hz, 1H, C*H*HNCO), 4.14 (deform ddd, *J* = 9.4, 9.2, 6.6 Hz, 1H, C*H*HOCO), 4.30 (deform ddd, *J* = 9.3, 9.2, 6.9 Hz, 1H, C*H*HOCO), 4.53 (dd, *J* = 11.6, 8.3 Hz, 1H, C*H*CON), 4.59 (dd, *J* = 10.4, 8.3 Hz, 1H, C*H*N), 6.05 (dd, *J* = 15.5, 10.4 Hz, 1H, C*H*CHN), 6.55 (d, *J* = 15.5 Hz, 1H, C*H*Ph), 7.21-7.37 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 13.5 (CHCH$_3$), 27.6 (CH_2CH_2N), 34.8 (CHCH$_3$), 42.6 (CH_2CCO_2Me), 43.5 (CH_2N), 48.9 (*C*HCON), 52.1 (CO_2CH_3), 56.1 (CH_2NCO), 62.0 (CH_2OCO), 64.9 (CHN), 80.0 (CCO_2Me), 126.6, 127.2, 128.7, 136.3 (Ar*C*), 128.0 (*C*HCHN), 134.7 (*C*HPh), 152.8 (NCO_2), 171.5 (CON), 175.5 (CCO_2Me); MS (EI-GC) *m/z*: 398 (M^+, <1%), 243 (11), 185 (15), 184 (100), 156 (16); HRMS calculated for $C_{22}H_{26}N_2O_5$ +1: 399.1920; found: 399.1934.

Methyl (3aS,4S*,8aR*,8bR*)-2-methyl-1,3-dioxo-4-[(E)-styryl]decahydropyrrolo[3,4-a]pyrrolizine-8a-carboxylate endo-* ***23ad***:[27] Sticky brown oil, 122 mg (69%); IR (neat) ν_{max} 2360, 2341, 1699, 1265 cm^{-1}; ^1H NMR δ_H: 1.73-1.85, 1.95-2.08 (m, 2H, C*H*$_2$CH$_2$N), 2.31-2.40, 2.46-2.59 (m, 3H, C*H*$_2$CCO$_2$Me, C*H*HN), 2.97 (s, 3H, NCH$_3$), 3.08 (m, 1H, C*H*HN), 3.46 (deform. dd, *J* = 8.1 Hz, 1H, C*H*CHN), 3.81 (s, 3H, CO_2CH_3), 3.89 (d, *J* = 8.1 Hz, 1H, CHCCO$_2$Me), 4.20 (dd, *J* = 9.0, 8.1 Hz, 1H, CHN), 6.37 (dd, *J* = 15.6, 9.0 Hz, 1H, C*H*CHN), 6.76 (d, *J* = 15.6 Hz, 1H, C*H*Ph), 7.21-7.42 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 25.0 (NCH$_3$), 25.3 (CH_2CH_2N), 30.3 (CH_2CCO_2Me), 48.3 (CH_2N), 51.2 (CHCCO$_2$Me), 52.3 (CHCHCCO$_2$Me),

53.2 (CCO_2CH_3), 64.6 (CHN), 78.9 (CCO_2CH_3), 123.4 (*C*HCHN), 126.9, 128.1, 128.6, 136.7 (Ar*C*), 135.9 (*C*HPh), 174.1, 176.7 (2xCON), 177.1 (CO_2Me); MS (EI-GC) *m/z*: 354 (M^+, <1%), 296 (25), 295 (100), 243 (30), 242 (10), 241 (10), 228 (11), 184 (13), 115 (12), 91 (11); Microanalysis calculated for $C_{20}H_{22}N_2O_4$: C, 67.8; H, 6.3; N, 7.9%; found: C, 68.2; H, 6.3; N, 8.0%.

Methyl (3aS,4S*,8aR*,8bR*)-2-methyl-1,3-dioxo-4-[(E)-styryl]decahydropyrrolo[3,4-a]pyrrolizine-8a-carboxylate exo-**23ad**:*[27] Sticky brown oil, 22 mg (12%); IR (neat) ν_{max} 2370, 2328, 1715 cm^{-1}; ^{1}H NMR δ_H: 1.83-2.02 (m, 3H, C*H*$_2$CH$_2$N, C*H*HCCO$_2$Me), 2.72-2.81(m, 1H, C*H*HCCO$_2$Me), 2.98 (s, 3H, NCH$_3$), 3.02-3.09 (m, 2H, CH$_2$N), 3.40 (d, *J* = 9.5 Hz, 1H, C*H*CCO$_2$Me), 3.56 (dd, *J* = 9.5, 7.5 Hz, 1H, C*H*CHN), 3.71 (s, 3H, CO_2CH_3), 4.42 (deform. dd, *J* = 7.5, 7.0 Hz, 1H, CHN), 6.32 (dd, *J* = 15.9, 7.0 Hz, 1H, C*H*CHN), 6.85 (d, *J* = 15.9 Hz, 1H, C*H*Ph), 7.22-7.42 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 25.0 (NCH$_3$), 25.3 (CH$_2$CH$_2$N), 36.3 (CH$_2$CCO$_2$Me), 49.3 (CH$_2$N), 51.1 (CHCCO$_2$Me), 52.7 (CHCHCCO$_2$Me), 57.1 (CCO_2CH_3), 67.3 (CHN), 78.8 (CCO_2CH_3), 125.3 (*C*HCHN), 126.7, 128.1, 128.6, 136.3 (Ar*C*), 134.9 (*C*HPh), 172.1, 176.1 (2xCON), 176.3 (CO_2Me); MS (EI-GC) *m/z*: 354 (M^+, <1%), 296 (31), 295 (100), 243 (28), 242 (11), 228 (15), 184 (12), 183 (10), 115 (14); Microanalysis calculated for $C_{20}H_{22}N_2O_4$: C, 67.8; H, 6.3; N, 7.9%; found: C, 68.6; H, 6.5; N, 8.1%.

Benzyl (3aS,4S*,8aR*,8bR*)-2-methyl-1,3-dioxo-4-[(E)-styryl]decahydropyrrolo[3,4-a]pyrrolizine-8a-carboxylate endo-**23bd***: Brown prisms, 149 mg, (60%), mp: 92-95 ºC; IR (neat) ν_{max} 2924, 1770, 1694 cm^{-1}; ^{1}H NMR δ_H: 1.80-1.85, 1.96-2.06 (m, 2H, C*H*$_2$CH$_2$N), 2.38 (ddd, *J* = 13.8, 9.5, 4.3 Hz, 1H, C*H*HCCO$_2$Me), 2.49 (ddd, *J* = 13.8, 8.9, 7.9 Hz, 1H, C*H*HCCO$_2$Me), 2.59 (deform. ddd, *J* = 9.4, 7.9, 7.8 Hz, 1H, C*H*HN), 2.99 (s, 3H, NCH$_3$), 3.07 (ddd, *J* = 9.4, 8.0, 3.4 Hz, 1H, C*H*HN), 3.46 (deform. dd, *J* = 8.2, 8.1 Hz, 1H, C*H*CHN), 3.85 (d, *J* = 8.1 Hz, 1H, CHCCO$_2$Me), 4.20 (deform. dd, *J* = 9.3, 8.2 Hz, 1H, CHN), 5.23 (d, *J* = 12.2 Hz, 1H, C*H*HPh), 5.29 (d, *J* = 12.2 Hz, 1H, C*H*HPh), 6.36 (dd, *J* = 15.6, 9.3 Hz, 1H, C*H*CHN), 6.74 (d, *J* = 15.6 Hz, 1H, C*H*Ph), 7.26-7.45 (m, 10H, Ar*H*); ^{13}C NMR δ_C: 25.2 (CH$_2$CH$_2$N), 25.3 (NCH$_3$), 30.0 (CH$_2$CCO$_2$Me), 48.0 (CH$_2$N), 51.0 (CHCCO$_2$Me), 52.5 (CHCHCCO$_2$Me), 64.3 (CHN), 67.5 (CH$_2$Ph), 78.8 (CCO_2CH_3), 123.6 (*C*HCHN), 126.9, 128.1, 128.3, 128.6, 128.7, 128.8, 135.7, 135.8 (Ar*C*), 136.7 (*C*HPh), 173.2, 176.7 (2xCON), 177.0 (CO_2Bn); MS (EI-GC) *m/z*: 430 (M^+, <1%), 185 (15), 184 (100), 156 (11); HRMS calculated for $C_{26}H_{26}N_2O_4$ +1:430.1971; found: 430.1953.

Benzyl (3aR,4S*,8aR*,8bS*)-2-methyl-1,3-dioxo-4-[(E)-styryl]decahydropyrrolo[3,4-a]pyrrolizine-8a-carboxylate exo-**23bd***: Yellow prisms, 19 mg (9%), mp: 85-87 ºC; IR (neat) ν_{max} 2934, 1699 cm^{-1}; ^{1}H NMR δ_H: 1.84-2.05 (m, 3H, C*H*HCCO$_2$Me, C*H*$_2$CH$_2$N), 2.68 (s, 3H, NCH$_3$), 2.70-2.79 (m, 1H, C*H*HCCO$_2$Me), 3.05-3.13 (m, 2H, CH$_2$N), 3.40 (d, *J* = 9.5 Hz, 1H, CHCCO$_2$Me), 3.56 (dd, *J* = 9.5, 8.2 Hz, 1H, CHN), 4.44 (ddd, *J* = 8.2, 6.8, 1.0 Hz, 1H, CHN), 5.12 (s, 2H, CH$_2$Ph), 6.34 (dd, *J* = 15.9, 6.8 Hz, 1H, C*H*CHN), 6.83 (d, *J* = 15.9 Hz, 1H, C*H*Ph), 7.25-7.45 (m, 10H, Ar*H*); ^{13}C NMR δ_C: 24.8 (NCH$_3$), 25.6 (CH$_2$CH$_2$N), 36.7 (CH$_2$CCO$_2$Me), 49.7 (CH$_2$N), 51.1 (CHCCO$_2$Me), 57.6 (CHCHCCO$_2$Me), 67.5 (CHN), 67.8 (CH$_2$Ph), 78.6 (CCO_2CH_3), 125.5 (*C*HCHN), 126.8, 128.2, 128.6, 128.8, 128.8, 128.9, 134.8, 135.2 (Ar*C*), 136.5 (*C*HPh), 171.6, 176.0 (2xCON), 176.3 (CO_2Bn); MS (EI-GC) *m/z*: 430 (M^+, <1%), 184 (45), 182 (12), 181 (100), 91 (10); HRMS calculated for $C_{26}H_{26}N_2O_4$ +1:430.1971; found: 430.1953.

Trimethyl (1R,2R*,3S*,7aR*)-3-[(E)-styryl]hexahydro-1H-pyrrolizine-1,2,7a-tricarboxylate endo-**23ae**:*[27] Sticky yellow oil, 137 mg (71%); IR (neat) ν_{max} 2965, 2915, 2306, 1715, 1713, 1699 cm^{-1}; ^{1}H NMR δ_H: 1.76–1.86 (m, 1H, C*H*HCH$_2$N), 1.93–2.03 (m, 1H, C*H*HCH$_2$N), 2.08–2.17 (m, 1H, C*H*HCCO$_2$Me), 2.52–2.61 (m, 1H, C*H*HCCO$_2$Me), 2.83 (deform. ddd, *J* = 10.8, 6.6, 6.5 Hz, 1H, C*H*HN), 3.09 (deform. ddd, *J* = 10.8, 6.6, 6.5 Hz, 1H, C*H*HN), 3.42 (d, *J* = 11.7 Hz, 1H, C*H*CCO$_2$Me), 3.58, 3.69 (s, 6H, 2xCHCO$_2$C*H*$_3$), 3.70 (s, 3H, CCO$_2$C*H*$_3$), 4.02 (dd, *J* = 11.7, 8.2 Hz, 1H, C*H*CHN), 4.28 (dd, *J* = 10.4, 8.2 Hz, 1H, C*H*N), 5.96 (dd, *J* = 15.5, 10.4 Hz, 1H, C*H*CHN), 6.56 (d, *J* = 15.5 Hz, 1H, C*H*Ph), 7.25-7.35 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 27.6 (CH$_2$CH$_2$N), 35.8 (CH$_2$CCO$_2$Me), 48.8 (CH$_2$N), 52.1, 52.2 (2x*C*HCO$_2$Me), 52.4, 52.6, 53.6 (3xCO$_2$*C*H$_3$), 65.7 (CHN), 78.2 (*C*CO$_2$Me), 125.3 (*C*HCHN), 126.7, 128.2, 128.7, 136.3 (Ar*C*), 135.8 (*C*HPh), 171.1, 171.7 (2xCHCO$_2$Me), 174.1 (CCO$_2$Me); MS (EI-GC) *m/z*: 387 (M^+, <1%), 271 (19), 270 (100), 243 (13), 238 (21), 210 (17), 184 (40), 123 (10), 115 (10); Microanalysis calculated for $C_{21}H_{25}NO_6$: C, 65.1; H, 6.5; N, 3.6 %; found: C, 65.4; H, 7.0; N, 3.9%.

*Exo-**25ae** could not be separated.*

Methyl (1S,2S*,3S*,7aR*)-2-nitro-1-phenyl-3-[(E)-styryl]hexahydro-1H-pyrrolizine-7a- carboxylate endo-**23af**:*[27] Sticky brown oil, 132 mg (67%); IR (neat) ν_{max} 3003, 2983, 2872, 1726, 1536 cm^{-1}; ^{1}H NMR δ_H: 1.86–2.10 (m, 3H, C*H*$_2$CH$_2$N, C*H*HCCO$_2$Me), 2.68-2.76 (m, 1H, C*H*HCCO$_2$Me), 2.92 (ddd, *J* = 10.1, 6.7, 4.5 Hz, 1H, C*H*HN), 3.25 (ddd, *J* = 10.1, 7.5, 6.3 Hz, 1H, C*H*HN), 3.37 (s, 3H, CCO$_2$CH$_3$), 4.17 (d, *J* = 11.3 Hz, 1H, C*H*CCO$_2$Me), 4.79 (dd, *J* = 10.2, 7.9 Hz, 1H, C*H*N), 6.10 (dd, *J* = 11.3, 7.8 Hz, 1H, C*H*NO$_2$), 6.14 (dd, *J* = 15.5, 10.3 Hz, 1H, C*H*CHN), 6.72 (d, *J* = 15.5 Hz, 1H, C*H*Ph), 7.23-7.40 (m, 10H, Ar*H*); ^{13}C NMR δ_C: 27.4 (CH$_2$CH$_2$N), 35.5 (CH$_2$CCO$_2$Me), 48.6 (CH$_2$N), 52,1 (CCO$_2$CH$_3$), 55.4 (CHCCO$_2$CH$_3$), 66.2 (CHN), 80.5 (CCO$_2$Me), 91.9 (CHNO$_2$), 122.7 (CHCHN), 127.1, 127.3, 128.3, 128.6, 128.7, 128.9, 134.1, 135.8 (Ar*C*), 138.3 (*C*HPh), 173.6 (CCO$_2$Me); MS (EI-GC) *m/z*: 392 (M^+, <1%), 243 (11), 185 (14), 184 (100), 156 (16); HRMS calculated for $C_{23}H_{24}N_2O_4$+1: 393.1814; found: 393.1800.

Methyl (1R,2S*,3S*,7aR*)-1-nitro-2-phenyl-3-[(E)-styryl]hexahydro-1H-pyrrolizine-7a-carboxylate endo-**24af**:*[27] Sticky brown oil, 23 mg (12%); IR (neat) ν_{max} 3015, 2979, 2872, 1725, 1530 cm^{-1}; ^{1}H NMR δ_H: 1.57-1.63 (m, 1H, C*H*HCH$_2$N), 1.96-2.02 (m, 2H, C*H*HCH$_2$N, C*H*HCCO$_2$Me), 2.46-2.52 (m, 1H, C*H*HCCO$_2$Me), 3.03 (ddd, *J* = 10.8, 8.7, 6.1 Hz, 1H, C*H*HN), 3.13-3.19 (m, 1H, C*H*HN), 4.06 (dd, *J* = 11.6, 10.2 Hz, 1H, C*H*Ph), 4.23 (ddd, *J* = 11.6, 7.6, 0.5 Hz, 1H, C*H*N), 5.94 (d, *J* = 10.2 Hz, 1H, C*H*NO$_2$), 6.18 (dd, *J* = 15.9, 7.6 Hz, 1H, C*H*CHN), 6.44 (dd, *J* = 15.9, 0.5 Hz, 1H, C*H*Ph), 7.24-7.40 (m, 10H, Ar*H*); ^{13}C NMR δ_C: 26.0 (CH$_2$CH$_2$N), 32.1 (CH$_2$CCO$_2$Me), 50.7 (CH$_2$N), 51.0 (CCO$_2$CH$_3$), 53.6 (*C*HPh), 67.8 (CHN), 76.2 (*C*CO$_2$Me), 97.1 (*C*HNO$_2$), 123.8 (*C*HCHN), 126.6, 127.9, 128.0, 128.2, 128.7, 129.2, 136.1, 136.2 (Ar*C*), 136.4 (*C*HPh), 173.5 (CCO$_2$Me); MS (EI-GC) *m/z*: 392 (M^+, <1%), 243 (10), 185 (15), 184 (100), 156 (17), 115 (10); HRMS calculated for $C_{23}H_{24}N_2O_4$+1: 393.1814; found: 393.1806.

Methyl (2S,3S*,7aR*)-2-(phenylsulfonyl)-3-[(E)-styryl]hexahydro-1H-pyrrolizine-7a-carboxylate endo-**23ag***: Brown prisms, 146 mg (71%), mp: 130-135 ºC; IR (neat) ν_{max} 2955, 2878, 1726, 1303, 1147 cm^{-1}; ^{1}H NMR δ_H: 1.74-1.93 (m, 3H, C*H*$_2$CH$_2$N, C*H*HCCO$_2$Me), 2.34-2.48 (m, 2H, C*H*HCCO$_2$Me, C*H*HN), 2.83-2.93 [m, 2H, C*H*HN, C*H*HCH(SO$_2$Ph)], 3.07-3.13 [m, 1H, C*H*HCH(SO$_2$Ph)], 3.74 (s, 3H, CO$_2$CH$_3$), 3.95 (dd, *J* = 10.2, 6.7 Hz, 1H, CHN), 4.20 [deform dt, *J* = 12.2, 6.7 Hz, 1H, C*H*(SO$_2$Ph)CH], 6.20 (dd, *J* = 15.6, 10.2 Hz, 1H, C*H*CHN), 6.30 (d, *J* = 15.6 Hz, 1H, C*H*Ph), 7.30-7.48 (m, 7H, Ar*H*), 7.60-7.64 (m, 1H, Ar*H*), 7.79-7.81 (m, 2H, Ar*H*); ^{13}C NMR δ_C: 27.6 (CH$_2$CH$_2$N), 35.0 (CH$_2$CCO$_2$Me), 37.2 (CH$_2$CCO$_2$Me), 48.1 (CH$_2$N), 52.8 (CO$_2$CH$_3$), 66.2 (CHN), 67.6 [CH(SO$_2$Ph)], 75.8 (CCO$_2$Me), 123.7 (CHCHN), 127.0, 128.2, 128.6, 128.8, 129.0, 133.8, 136.4, 139.3 (Ar*C*), 136.0 (*C*HPh), 176.0 (CCO$_2$Me); MS (EI-GC) *m/z*: 411 (M^+, <1%), 239 (15), 238 (100), 210 (10), 96 (21), 77 (10); HRMS calculated for $C_{23}H_{25}NO_4S$ +1: 412.1582; found: 412.1589.

*Exo-**23ag** could not be separated.*

Methyl (1R,2R*,3S*,7aS*)-1,2-bis(phenylsulfonyl)-3-[(E)-styryl]hexahydro-1H-pyrrolizine-7a-carboxylatetricarboxylate endo-**23ah**:*[27] Sticky pale yellow oil, 183 mg (66%); IR (neat) ν_{max} 2991, 2934, 1708, 1310, 1141 cm^{-1}; ^{1}H NMR δ_H: 1.99–2.05 (m, 2H, C*H*$_2$CH$_2$N), 2.14-2.22 (m, 1H, C*H*HCCO$_2$Me), 3.03-3.07 (m, 1H, C*H*HCCO$_2$Me), 3.14-3.21 (m, 1H, C*H*HN), 3.32-3.38 (m, 1H, C*H*HN), 3.87 (s, 3H, CCO$_2$CH$_3$), 4.51 (d, *J* = 8.1 Hz, 1H, C*H*CCO$_2$Me), 4.71 (dd, *J* = 10.0, 8.2 Hz, 1H, CHN), 5.04 (deform. dd, *J* = 8.2, 8.1 Hz, 1H, CHN), 6.20 (d, *J* = 15.7 Hz, 1H, C*H*Ph), 6.47 (dd, *J* = 15.7, 10.0 Hz, 1H, C*H*CHN), 7.13-8.04 (m, 15H, Ar*H*); ^{13}C NMR δ_C: 25.6 (CH$_2$CH$_2$N), 35.1 (CH$_2$CCO$_2$Me), 49.1 (CH$_2$N), 53.1 (CHCO$_2$CH$_3$), 65.7 (CHN), 73.7 [CH(SO$_2$Ph)CH], 74.5 [CH(SO$_2$Ph)CCO$_2$Me], 78.8 (CCO$_2$Me), 122.7 (CHCHN), 126.9, 128.3, 128.6, 128.9, 129.0, 129.6, 133.6, 133.9, 134.5, 135.9, 139.2, 141.5 (Ar*C*), 136.7 (*C*HPh), 170.9 (CCO$_2$Me); MS (EI-GC) *m/z*: 493 (10), 492 (11), 410 (10), 310 (11), 244 (31), 243 (100), 128 (15), 115 (17); HRMS calculated for $C_{29}H_{29}NO_6S_2$ +1: 552.1514; found: 552.1548.

Methyl (1S,2S*,3S*,7aS*)-1,2-bis(phenylsulfonyl)-3-[(E)-styryl]hexahydro-1H-pyrrolizine-7a-carboxylate exo-**23ah**:*[27] Sticky yellow oil, 28 mg (10%);

IR (neat) ν_{max} 2979, 2910, 1715, 1300, 1148 cm^{-1}; ^1H NMR δ_H: 2.02–2.17 (m, 3H, C*H*$_2$CH$_2$N, C*H*HCCO$_2$Me), 2.94-3.16 (m, 3H, C*H*HCCO$_2$Me, CH$_2$N), 3.83 (s, 3H, CCO$_2$CH$_3$), 4.03 (deform dd, *J* = 4.3, 4.1 Hz, 1H, C*H*(SO$_2$Ph)CH), 4.38 (dd, *J* = 8.4, 4.3 Hz, 1H, CHN), 5.06 (d, *J* = 4.1 Hz, 1H, C*H*(SO$_2$Ph)CCO$_2$Me), 6.13-6.24 (m, 2H, C*H*CHN, C*H*Ph), 7.14-7.90 (m, 15H, Ar*H*); ^{13}C NMR δ_C: 26.4 (CH$_2$CH$_2$N), 32.4 (CH$_2$CCO$_2$Me), 47.2 (CH$_2$N), 53.3 (CHCO$_2$CH$_3$), 64.7 (CHN), 66.9 [CH(SO$_2$Ph)CH], 71.7 [CH(SO$_2$Ph)CCO$_2$Me], 79.8 (CCO$_2$Me), 125.9 (*C*HCHN), 126.7, 128.2, 128.6, 128.9, 128.9, 129.3, 129.3, 134.2, 134.3, 135.7, 137.0, 138.5 (Ar*C*), 135.2 (*C*HPh), 173.9 (C*C*O$_2$Me); MS (EI-GC) *m/z*: 551 (M^+, <1%), 492 (15), 410 (10), 311 (10), 310 (10), 244 (25), 243 (100), 128 (11), 115 (21); HRMS calculated for $C_{29}H_{29}NO_6S_2$ +1: 552.1514; found: 552.1565.

Dimethyl (2S,3S*,7aR*)-3-[(E)-prop-1-en-1-yl]hexahydro-1H-pyrrolizine-2,7a-dicarboxylate endo-**25aa***:[27] Sticky brown oil, 113 mg (85%); IR (neat) ν_{max} 2985, 2939, 2305, 1714, 1691 cm^{-1}; ^1H NMR δ_H: 1.69 (d, *J* = 6.5 Hz, 3H, CHC*H*$_3$), 1.71–1.85 (m, 3H, C*H*$_2$CH$_2$N, C*H*HCCO$_2$Me), 2.02-2.12 (m, 1H, C*H*HCO$_2$Me), 2.20-2.23 (m, 1H, C*H*HCHCO$_2$Me), 2.55 (dd, *J* = 13.2, 6.7 Hz, 1H, C*H*HCHCO$_2$Me), 2.79-2.87 (m, 1H, C*H*HN), 3.02-3.07 (m, 1H, C*H*HN), 3.41 (deform. ddd, *J* = 12.7, 7.5, 6.7 Hz, 1H, C*H*CO$_2$Me), 3.61 (s, 3H, CHCO$_2$C*H*$_3$), 3.72 (s, 3H, CCO$_2$C*H*$_3$), 3.99 (dd, *J* = 10.3, 7.5 Hz, 1H, C*H*N), 5.25 (dd, *J* = 15.0, 10.3 Hz, 1H, C*H*CHN), 5.68 (dq, *J* = 15.0, 6.5 Hz, 1H, C*H*Me); ^{13}C NMR δ_C: 17.9 (CHCH$_3$), 27.6 (CH$_2$CH$_2$N), 36.4 (CH$_2$CHCO$_2$Me), 37.1 (CH$_2$CCO$_2$Me), 48.6 (CH$_2$N), 49.8 (CHCO$_2$Me), 51.7 (CHCO$_2$CH$_3$), 52.6 (CCO$_2$CH$_3$), 67.3 (CHN), 76.3 (CCO$_2$Me), 126.8 (CHCHN), 132.1 (*C*HMe), 172.5 (CHCO$_2$Me), 177.0 (CCO$_2$Me); MS (EI-GC) *m/z*: 267 (M^+, <1%), 208 (100), 207 (10), 181 (25), 59 (10); Microanalysis calculated for $C_{14}H_{21}NO_4$: C, 62.9; H, 7.9; N, 5.2%; found: C, 63.3; H, 7.4; N, 5.4%.

2-Allyl 7a-methyl (2S,3S*,7aR*)-2-methyl-3-[(E)-prop-1-en-1-yl]hexahydro-1H-pyrrolizine-2,7a-dicarboxylate endo-**25ab***: Pale yellow needles, 130 mg (85%), mp 107-108 ºC (hexanes/AcOEt); IR (neat) ν_{max} 2980, 2935, 2315, 1715, 1690 cm^{-1}; ^1H NMR δ_H: 1.36 (s, 3H,C*H*$_3$), 1.68 (dd, *J* = 1, and 6.5 Hz, 3H, CHC*H*$_3$), 1.71–2.00 (m, 3H, C*H*$_2$CH$_2$N, C*H*HCCO$_2$Me), 2.15 (m, 1H, C*H*HCO$_2$Me), 2.42, 2.53 (2d, *J* = 13.5 Hz, 2H, CH$_2$CMeCO$_2$Me), 2.90, 3.05 (2m, 2H, CH$_2$N), 3.52 (d, *J* = 10 Hz, 1H, C*H*N), 3.74 (s, 3H, CHCO$_2$C*H*$_3$), 4.51 (d, *J* = 6 Hz, 2H, CH$_2$O), 5.19-5.35 (m, 3H, CH=CH$_2$), 5.64, 5.85 (2m, 2H, HC=CH); ^{13}C NMR δ_C: 8.9 (CH*C*H$_3$), 27.5 (*C*H$_2$CH$_2$N), 30.9 (C*C*H$_3$), 35.7 (CH$_2$CCO$_2$Me), 45.7 (O*C*H$_3$), 48.7 (CH$_2$N),52.1 [CH$_2$C(CH$_3$)CO$_2$Allyl], 53.4(CHN),65.6 (CO$_2$CH$_2$CHCH$_2$), 78.1 [*C*(CH$_3$)CO$_2$Allyl],125.6 (CO$_2$CH$_2$CH*C*H$_2$), 126.6 (*C*HCHN),128.8 (*C*HCHCHN), 135.7 (*C*HMe), 136.2 (CO$_2$CH$_2$*C*HCH$_2$), 171.5, 174.0 (2xCO).MS (EI-GC) *m/z*: 307 (M^+, 2%); Microanalysis calculated for $C_{17}H_{25}NO_4$: C, 66.4; H, 8.2; N, 4.6%; found: C, 66.3; H, 7.9; N, 4.4%.

Dimethyl (2S,3R*,7aR*)-3-phenylhexahydro-1H-pyrrolizine-2,7a-dicarboxylate endo-**26aa***:[27] Sticky colorless oil, 103 mg (68%); IR (neat) ν_{max} 2900, 1718, 1687 cm^{-1}; ^1H NMR δ_H: 1.81–2.00 (m, 3H, C*H*$_2$CH$_2$N, C*H*HCCO$_2$Me), 2.34-2.43 (m, 2H, C*H*HCCO$_2$Me, C*H*HCHCO$_2$Me), 2.54-2.61 (m, 1H, C*H*HCHCO$_2$Me), 2.64-2.76 (m, 2H, CH$_2$N), 3.23 (s, 3H, CHCO$_2$C*H*$_3$), 3.76 (s, 3H, CCO$_2$C*H*$_3$), 3.88 (ddd, *J* = 13.0, 8.8, 7.4 Hz, 1H, CHCO$_2$Me), 4.73 (d, *J* = 8.8 Hz, 1H, CHN), 7.15-7.17, 7.25-7.28 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 28.3 (CH$_2$CH$_2$N), 36.3 (CH$_2$CHCO$_2$Me), 36.7 (CH$_2$CCO$_2$Me), 47.2 (CH$_2$N), 51.4 (*C*HCO$_2$Me), 52.7 (CHCO$_2$CH$_3$), 52.5 (CCO$_2$CH$_3$), 67.3 (CHN), 76.1 (CCO$_2$Me), 127.9, 128.2, 129.3, 138.0 (Ar*C*), 172.2 (CH*C*O$_2$Me), 177.3 (C*C*O$_2$Me); MS (EI-GC) *m/z*: 303 (M^+, <1%), 245 (11), 244 (100), 226 (21), 218 (10), 217 (17), 185 (26), 77 (15); HRMS calculated for $C_{17}H_{21}NO_4$ +1: 304.1549; found: 304.1553.

Dimethyl (3R,7aR*)-3-phenylhexahydro-1H-pyrrolizine-1,7a-dicarboxylate **27aa***:[27] Sticky colorless oil, 26 mg (16%); IR (neat) ν_{max} 2935, 2903, 1720, 1705 cm^{-1}; ^1H NMR δ_H: 1.37–1.48 (m, 1H, C*H*HCCO$_2$Me), 1.65-1.86 (m, 2H, C*H*$_2$CH$_2$N), 2..18 (ddd, *J* = 12.1, 6.7, 4.1 Hz, 1H, C*H*HCHPh), 2.26-2.34 (m, 1H, C*H*HCCO$_2$Me), 2.41-2.55 (m, 3H, C*H*HCHPh, C*H*$_2$N), 3.72 (s, 3H, CHCO$_2$C*H*$_3$), 3.82 (s, 3H, CCO$_2$C*H*$_3$), 3.80 (dd, *J* = 12.1, 6.7 Hz, 1H, CHCO$_2$Me), 4.49 (dd, *J* = 12.8, 4.0 Hz, 1H, CHN), 7.27-7.45 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 25.8 (CH$_2$CH$_2$N), 29.2 (*C*H$_2$CHPh), 33.0 (CH$_2$CCO$_2$Me), 50.7 (CH$_2$N), 51.0 (*C*HCO$_2$Me), 52.0 (CHCO$_2$CH$_3$), 52.9 (CCO$_2$CH$_3$), 64.8 (CHN), 76.4 (CCO$_2$Me), 127.7, 128.3, 128.9, 137.7 (Ar*C*), 173.1 (CH*C*O$_2$Me), 175.5 (C*C*O$_2$Me); MS (EI-GC) *m/z*: 303 (M^+, <1%), 245 (10), 244 (100), 243 (10), 227 (10), 226 (23), 217 (14), 185 (15), 77 (13); HRMS calculated for $C_{17}H_{21}NO_4$ +1: 304.1549; found: 304.1592.

Dimethyl (2S,3S*,7aR*)-3-isobutylhexahydro-1H-pyrrolizine-2,7a-dicarboxylate endo-**28aa***:[27] Colorless oil, 90 mg (80%); IR (neat) ν_{max} 2986, 2956, 2903, 1716, 1700 cm^{-1}; ^1H NMR δ_H: 0.93 [d, 6H, *J* = 6.0 Hz, CH(C*H*$_3$)$_2$], 1.35-1.41 [m, 2H, C*H*HCH$_2$N, C*H*(CH$_3$)$_2$], 1.52-1.62 (m, 1H, C*H*HCH$_2$N), 1.74-1.83, 1.87-1.94 (m, 2H, C*H*$_2$CCO$_2$Me), 2.22 (dd, *J* = 13.7, 5.4 Hz, 1H, C*H*HCHCO$_2$Me), 2.41 (ddd, *J* = 12.6, 8.4, 4.0 Hz, 1H, C*H*HCHCO$_2$Me), 2.57 (dd, *J* = 13.7, 9.1 Hz, 1H, C*H*HCHCO$_2$Me), 2.92-3.15 (m, 3H, C*H*N, C*H*HN, C*H*CO$_2$Me), 3.68 (s, 3H, CHCO$_2$CH$_3$), 3.73 (s, 3H, CCO$_2$CH$_3$); ^{13}C NMR δ_C: 22.9 [CH(*C*H$_3$)$_2$], 25.0 (CH$_2$CH$_2$N), 26.1 [CH(CH$_3$)$_2$], 35.8 (CH$_2$CHN) 37.8 (CH$_2$CCO$_2$Me), 39.7 (CH$_2$CHCO$_2$Me), 47.4 (CH$_2$N), 48.6 (CHCO$_2$CH$_3$), 51.5 (CCO$_2$*C*H$_3$), 52.9 (*C*HCO$_2$Me), 62.9 (CHN), 76.1 (*C*CO$_2$Me), 176.2 (CH*C*O$_2$Me), 176.3 (C*C*O$_2$Me); MS (EI-GC) *m/z*: 283 (M^+, <1%), 225 (15), 224 (100), 198 (14), 197 (35), 165 (21), 128 (11), 127 (10); Microanalysis calculated for $C_{15}H_{25}NO_4$: C, 63.6; H, 8.9; N, 4.9%; found: C, 63.5; H, 8.4; N, 5.1%.

Ethyl 1,7a-dimethyl (1S,3R*,7aR*)-hexahydro-1H-pyrrolizine-1,3,7a-tricarboxylate exo-**29aa***:[27] Sticky yellow oil, 88 mg (59%); IR (neat) ν_{max} 2991, 2910, 1714, 1711, 1699 cm^{-1}; ^1H NMR δ_H: 1.30 (t, *J* = 7.1 Hz, 3H, CO$_2$CH$_2$C*H*$_3$), 1.41 (ddd, *J* = 12.7, 11.4, 7.6 Hz, 1H, C*H*HCCO$_2$Me), 1.80-1.90 (m, 2H, CH$_2$N), 2.15 (ddd, *J* = 12.7, 7.0, 4.8 Hz, 1H, C*H*HCHCO$_2$Et), 2.32-2.47 (m, 2H, C*H*HCHCO2Et, C*H*HCCO$_2$Me), 2.52-2.61 (m, 1H, C*H*HN), 3.11-3.16 (m, 1H, C*H*HN), 3.59 (dd, *J* = 12.2, 7.0 Hz, 1H, CHCO$_2$Me), 3.69 (s, 3H, CHCO$_2$C*H*$_3$), 3.76 (s, 3H, CCO$_2$C*H*$_3$), 4.00 (dd, *J* = 12.2, 4.8 Hz, 1H, CHCO$_2$Et), 4.24 (q, *J* = 7.1 Hz, 2H, CO$_2$C*H*$_2$CH$_3$); ^{13}C NMR δ_C: 14.3 (CO$_2$CH$_2$CH$_3$), 26.0 (CH$_2$CH$_2$N), 28.8 (CH$_2$CHCO$_2$Et), 32.4 (CH$_2$CCO$_2$Me), 50.3 (CHCO$_2$Me), 51.4 (CO$_2$CH$_2$CH$_3$), 52.1 (CHCO$_2$CH$_3$), 52.9 (CCO$_2$CH$_3$), 61.3 (CH$_2$N), 64.7 (CHN), 76.7 (CCO$_2$Me), 169.9, 172.3, 174.7 (2xCO$_2$Me, CO$_2$Et); MS (EI-GC) *m/z*: 299 (M^+, <1%), 241 (14), 240 (100), 226 (21), 212 (23), 166 (10), 108 (21); HRMS calculated for $C_{23}H_{24}N_2O_4$ +1:300.1447; found: 300.1451.

1-Allyl 3-ethyl 7a-methyl (1S,3R*,7aR*)-1-methylhexahydro-1H-pyrrolizine-1,3,7a-tricarboxylate exo-**29ab***: Sticky yellow oil, 63 mg (37%); IR (neat) ν_{max} 2992, 1721, 1703, 2312 cm^{-1}; ^1H NMR δ_H: 1.22-1.47 (m, 8H, CO$_2$CH$_2$C*H*$_3$, C*H*$_2$CH$_2$N, CCH$_3$), 1.55-1.68 (m, 1H, C*H*HCCO$_2$Me), 1.87 (dd, *J* = 13.0, 5.4 Hz, 1H, C*H*HCCO$_2$Me), 2.48-2.58 (m, 1H, C*H*HC(CH$_3$)CO$_2$Allyl], 2.68-2.86 [m, 2H, C*H*HC(CH$_3$)CO$_2$Allyl, C*H*HN], 3.11-3-17 (m, 1H, C*H*HN), 3.75 (s, 3H, CCO$_2$CH$_3$), 4.14-4.29 (m, 3H, CHN, CO$_2$C*H*$_2$CH$_3$), 4.51-4.70 (m, 2H, CO$_2$C*H*$_2$CHCH$_2$), 5.26 (ddd, *J* = 10.5, 2.4, 1.3 Hz, 1H, CO$_2$CH$_2$CHC*H*H), 5.40 (ddd, *J* = 17.2, 2.4, 1.5 Hz, 1H, CO$_2$CH$_2$CHC*H*H), 5.94 (deform. dddd, *J* = 17.2, 10.5, 5.8, 5.6 Hz, 1H, CO$_2$CH$_2$C*H*CH$_2$); ^{13}C NMR δ_C: 14.2 (CO$_2$CH$_2$CH$_3$), 22.0 (CCH$_3$), 25.5 (CH$_2$CH$_2$N), 34.8 (CH$_2$CCO$_2$Me), 37.8 [CH$_2$C(CH$_3$)CO$_2$Allyl], 50.3 (CH$_2$N), 52.1 (CCO$_2$CH$_3$), 54.2 [*C*(CH$_3$)CO$_2$Allyl], 61.0 (CO$_2$CH$_2$CH$_3$), 63.1 (CHN), 65.7 (CO$_2$CH$_2$CHCH$_2$), 82.0 (CCO$_2$CH$_3$), 118.3 (CO$_2$CH$_2$CHCH$_2$), 131.8 (CO$_2$CH$_2$CHCH$_2$), 170.8 (CO$_2$Et), 173.8 (CO$_2$Allyl), 174.0 (CO$_2$Me); MS (EI-GC) *m/z*: 339 (M^+, <1%), 281 (18), 280 (100), 266 (16), 122 (26); HRMS calculated for $C_{17}H_{25}NO_6$ +1: 340.1760; found: 340.1770.

*Endo-**30aa** could not be separated.*

2-Allyl 3-ethyl 7a-methyl (2S,3R*,7aR*)-2-methylhexahydro-1H-pyrrolizine-2,3,7a-tricarboxylate endo-**30ab***: Sticky yellow oil, 30 mg (18%); IR (neat) ν_{max} 2996, 1715, 1698, 2317, 1291 cm^{-1}; ^1H NMR δ_H: 1.27 (t, *J* = 7.1 Hz, 3H, CO$_2$CH$_2$C*H*$_3$), 1.44 (s, 3H, CCH$_3$), 1.80-2.17 (m, 4H, C*H*$_2$CH$_2$N, C*H*$_2$CCO$_2$Me), 2.52 [d, *J* = 13.2 Hz, 1H, C*H*HC(CH$_3$)CO$_2$Allyl], 2.81 [d, *J* = 13.2 Hz, 1H, C*H*HC(CH$_3$)CO$_2$Allyl], 2.80-2.88 (m, 1H, C*H*HN), 3.18 (ddd, *J* = 10.6, 7.7, 4.3 Hz, 1H, C*H*HN), 3.74 (s, 3H, CCO$_2$CH$_3$), 3.89 (s, 1H, CHN), 4.07-4.21 (m, 2H, CO$_2$C*H*$_2$CH$_3$), 4.47-4.63 (m, 2H, CO$_2$C*H*$_2$CHCH$_2$), 5.23 (ddd, *J* = 10.4, 2.5, 1.2 Hz, 1H, CO$_2$CH$_2$CHC*H*H), 5.31 (ddd, *J* = 17.2, 2.5, 1.5 Hz, 1H, CO$_2$CH$_2$CHC*H*H), 5.87 (deform. dddd, *J* = 17.2, 10.4, 5.9, 5.8 Hz, 1H, CO$_2$CH$_2$C*H*CH$_2$); ^{13}C NMR δ_C: 14.3 (CO$_2$CH$_2$CH$_3$), 25.1 (CCH$_3$), 27.2 (CH$_2$CH$_2$N), 38.1 (CH$_2$CCO$_2$Me), 43.5 [CH$_2$C(CH$_3$)CO$_2$Allyl], 49.4 (CH$_2$N), 52.6 (CCO$_2$CH$_3$), 55.8 [*C*(CH$_3$)CO$_2$Allyl], 60.8 (CO$_2$CH$_2$CH$_3$), 65.7 (CO$_2$CH$_2$CHCH$_2$), 72.8 (CHN), 77.4 (CCO$_2$CH$_3$), 118.6 (CO$_2$CH$_2$CHCH$_2$), 131.9 (CO$_2$CH$_2$CHCH$_2$), 173.1 (CO$_2$Et), 174.5 (CO$_2$Allyl), 177.8 (CO$_2$Me); MS (EI-GC) *m/z*: 339 (M^+, <1%), 281 (18), 280 (100), 266 (28), 122 (24); HRMS calculated for $C_{17}H_{25}NO_6$ +1: 340.1745; found: 340.1760.

3-Ethyl 1,2,7a-trimethyl (1S,2S*,3R*,7aR*)-hexahydro-1H-pyrrolizine-1,2,3,7a-tetracarboxylate exo-**29ac***: colorless oil, 143 mg (80%); IR (neat) ν_{max} 2965, 1755, 1735 cm^{-1}; ^1H NMR δ_H: 1.27 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.00-2.15 (m, 3H, CH_2CH_2N, $CHHCO_2Me$), 2.52-2.60 (m, 1H, $CHHCO_2Me$), 2.77 (ddd, *J* = 9.7, 5.7, 2.2 Hz, 1H, CHHN), 3.02 (ddd, *J* = 9.7, 5.5, 2.5 Hz, 1H, CHHN), 3.67, 3.68, 3.69 (3s, 9H, CO_2CH_3, 2x$CHCO_2CH_3$), 3.69 (d, *J* = 11.8 Hz, 1H, $CHCO_2Me$), 4.15 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.15 (dd, *J* = 11.8, 7.9 Hz, 1H, $CHCO_2Me$), 4.28 (d, *J* = 7.9 Hz, 1H, $CHCO_2Et$); ^{13}C NMR δ_C: 14.3 ($CO_2CH_2CH_3$), 28.3 (CH_2CH_2N), 35.3 (CH_2CCO_2Me), 48.9 ($CO_2CH_2CH_3$), 50.0, 52.3 (2x$CHCO_2Me$), 52.3, 52.5, 53.2 (3xCO_2CH_3), 61.2 (CH_2N), 65.5 (CHN), 78.9 (CCO_2Me), 170.1, 171.0, 171.5, 174.0 (3xCO_2Me, CO_2Et); MS (EI-GC) *m/z*: 357 (M^+, <1%), 299 (17), 298 (100), 284 (17), 266 (62), 252 (17), 238 (49), 224 (16), 206 (12), 192 (41), 166 (47), 134 (43), 107 (10), 106 (17); HRMS calculated for $C_{16}H_{23}NO_8$ +1:358.1502; found: 358.1485.

3-Ethyl 1,2,7a-trimethyl (1R,2R*,3R*,7aR*)-hexahydro-1H-pyrrolizine-1,2,3,7a-tetracarboxylate endo-**29ac***: colorless oil, 143 mg (80%); IR (neat) ν_{max} 2960, 1751, 1733 cm^{-1}; ^1H NMR δ_H: 1.30 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.48 (ddd, *J* = 12.9, 11.0, 7.9 Hz, 1H, $CHHCCO_2Me$), 1.81-1.89 (m, 2H, CH_2CH_2N), 2.45-2.49 (m, 1H, $CHHCCO_2Me$), 2.59-2.66 (m, 1H, CHHN), 3.07-3-14 (m, 1H, CHHN), 3.64-3.71 (m, 1H, $CHCO_2CH_3$), 3.72, 3.73, 3.80 (3s, 9H, CCO_2CH_3, 2x$CHCO_2CH_3$), 3.91 (d, *J* = 11.4 Hz, 1H, $CHCO_2Me$), 4.23-4.28 (m, 3H, CHN, $CO_2CH_2CH_3$); ^{13}C NMR δ_C: 14.2 ($CO_2CH_2CH_3$), 25.6 (CH_2CH_2N), 32.7 (CH_2CCO_2Me), 46.6, 52.4 (2x$CHCO_2Me$), 51.7 ($CO_2CH_2CH_3$), 52.6, 53.2, 54.5 (3xCO_2CH_3), 61.7 (CH_2N), 65.6 (CHN), 76.6 (CCO_2Me), 168.6, 171.1, 172.0, 173.9 (3xCO_2Me, CO_2Et); MS (EI-GC) *m/z*: 357 (M^+, <1%), 299 (17), 298 (100), 284 (12), 267 (10), 266 (64), 252 (10), 238 (25), 192 (25), 166 (37), 134 (34), 106 (12); HRMS calculated for $C_{16}H_{23}NO_8$ +1:358.1502; found: 358.1491.

Ethyl (5*R*,5a*R*,8a*S*,8b*S*)-7-methyl-6,8-dioxo-5-[(*E*)-styryl]hexahydro-3*H*-pyrrolo[3',4':3,4]pyrrolo[1,2-*c*]thiazole-8b(1*H*)-carboxylate *endo*-**31**: colorless oil, 102 mg (63%); IR (neat) ν_{max} 2960, 1759, 1733 cm^{-1}; ^1H NMR δ_H: 3.01 (s, 3H, NCH_3), 3.12 (d, 1H, *J* = 11.0 Hz, CCH_2), 3.44 (d, *J* = 11Hz, CCH_2), 3.55-3.65 (d, *J* = 8.4 Hz 1H, CCH) 3.67-3.70 (m, 1H, NCHCH), 3.84 (s, 3H, CO_2CH_3), 3.93 (d, 1H, J = 7.2 Hz, NCH_2S), 3.97 (d, 1H, J = 7.2 Hz, NCH_2S), 4.40 (dd, *J* = 8.6, 0.8 Hz, 1H, NCH), 5.95 (dd, *J* = 15.5, 9.7 Hz, 1H, CHCH=), 6.72 (d, *J* = 15.5 Hz, 1H, =CHPh)7.19-7.47 (m, 5ArH); ^{13}C NMR δ_C: 25.2 (NCH_3), 35.2 (SCH_2C), 48.1 (CCHC), 48.9 (NCHCH), 52.4 (CO_2CH_3), 53.0 (SCH_2N), 63.2 (NCH), 79.5 (NC), 124.0, 126.9, 128.2, 128.6, 128.7, 135.9, 136.0 (ArC), 171.9 (CO_2), 174.6 (CO), 174.9(CO), MS (EI-GC) *m/z*: 372 (M^+, 7%), 325(11), 314(20), 313(100), 281(20), 115(18), 91(11); HRMS calculated for $C_{19}H_{20}N_2O_4S$: 372.1144; found: 372.1153.

*Exo-**31**could was lost during the separation.*

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