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Diastereoselective [3+2] *vs* [4+2] Cycloadditions of Nitroprolinates with α,β-Unsaturated Aldehydes and Electrophilic Alkenes: An Example of Total Periselectivity

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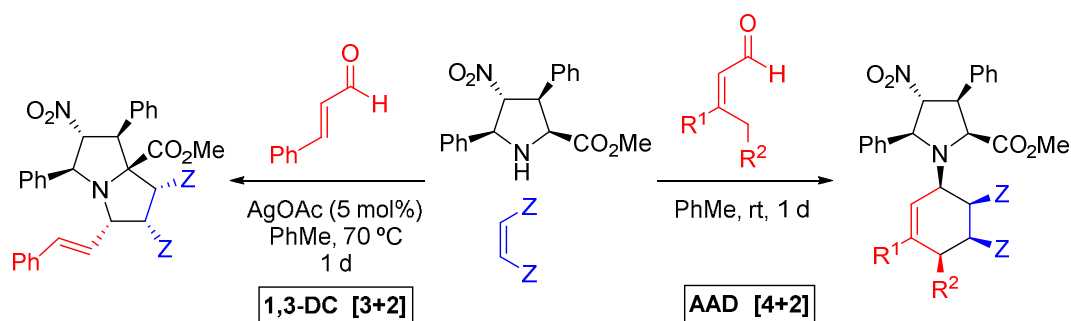[c] *Instituto de Síntesis Orgánica (ISO).*
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ABSTRACT: Diastereoselective multicomponent reaction of enantioenriched 4-nitroprolinates, obtained by enantiocatalyzed 1,3-dipolar cycloaddition (1,3-DC) of imino esters and nitroalkenes, with α,β-unsaturated aldehydes and electrophilic alkenes proceed with total periselectivity depending on the structure of the aldehyde employed. This process evolves through a [3+2] 1,3-DC when cinnamaldehyde is used in the presence of an azomethine ylide giving the corresponding highly substituted pyrrolizidines with *endo*-selectivity. However, in the case of the α,β-unsaturated aldehyde, which contains a hydrogen atom at the γ-position an amine-aldehyde-dienophile (AAD) [4+2] cycloaddition takes place by formation of an intermediate 1-amino-1,3-diene affording highly functionalized cyclohexenes with high *endo*-diastereoselectivity. This AAD process only occurred when a nitro group is bonded to the 4-position of the initial enantiomerically enriched pyrrolidine ring. DFT calculations have been done with the aim to explain this different behavior between pyrrolidines bearing or not a nitro group demonstrating the strongly nitro group-dependent

periselectivity. The results of these computational studies also support the experimentally obtained absolute configuration of the final adducts.

O₂N / Ph structure — 1,3-DC [3+2] product (left); central pyrrolidine: O₂N, Ph, Ph, CO₂Me, Z, Z; AAD [4+2] product (right): O₂N, Ph, Ph, CO₂Me, R¹, R², Z, Z.

Reagents left: AgOAc (5 mol%), PhMe, 70 °C, 1 d — **1,3-DC [3+2]**

Reagents right: PhMe, rt, 1 d — **AAD [4+2]**

INTRODUCTION

Diversity-oriented synthesis (DOS) concept described by Schreiber [1] has been interestingly applied in many methodologies for the synthesis of complex molecules. The formation of molecular frameworks, just by modifying functional group arrangements, reaction parameters, etc., are key features of divergent synthesis. In this concept, the addition of operational simplicity and atom (and step) economy provided by multicomponent reactions (MCRs) [2] constitutes a very important strategy. Particularly, 1,3-dipolar cycloadditions (1,3-DC) [3,4] and amide-aldehyde-dienophile (AAD) [5] are attractive and versatile multicomponent processes that can generate organic molecules with very different skeletons.

We and other groups have recently described that 1,3-DC of *in situ* generated cyclic azomethine ylides could be used for the generation of highly substituted

pyrrolizidines,[6] and indolizidines.[7,8] Namely, pyrrolizidine alkaloids are currently of special interest because they have wide and interesting biological properties. These heterocycles **2** can be obtained by multicomponent reaction of proline derived esters **1** with aromatic, aliphatic, and α,β-unsaturated aldehydes, and the corresponding dipolarophiles.[6,9] Mild reaction conditions were required for all type of electrophilic alkenes affording diastereoselectively bicyclic alkaloids **2** in good yields (Scheme 1, eq a).

On the other hand, the MCR known as AAD has been widely studied for the synthesis of 3-aminocyclohexenes and other interesting structures.[10] Amides, carbamates and sulfonamides reacted with aldehydes and dienophiles in the presence of TsOH through a [4+2] process, to yield the corresponding cycloadducts **3** (Scheme 1, eq b). These AAD reactions have provided the access to several hetero- and carbocycles as well as key structural cores of the natural product pumiliotoxin C.[11]

eq a)

X = CH$_2$, CHOH, S

eq b)

PG = RCO, ROCO, SO$_2$R
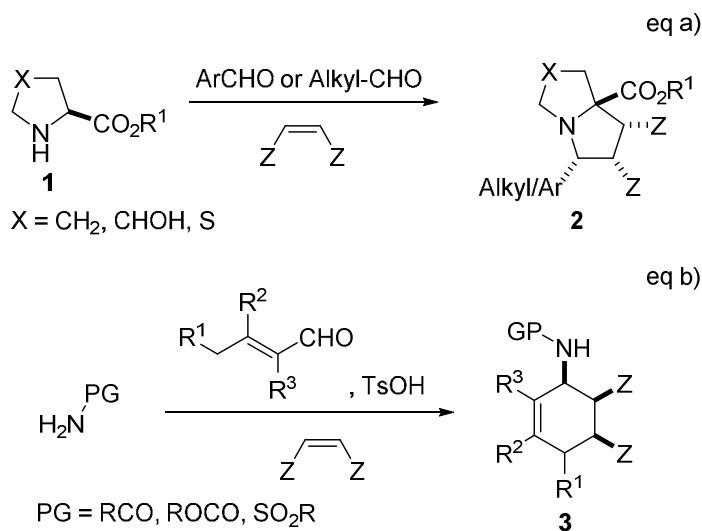
Scheme 1. a) General multicomponent 1,3-DC of prolinates, aldehydes and dipolarophiles affording pyrrolizidines **2**. b) General multicomponent [4+2]

cycloaddition of amides-aldehydes-dienophiles (AAD processes) providing 3-aminocyclohexenes **3**.

Concerning the presence of a nitro group in cyclic structures[12] not only allows a series of synthetic transformations but also enhances/modifies the biological properties of such molecules. Thus, optically active polysubstituted nitroprolinates have emerged as promising therapeutic agents. For example, molecules **4** (Figure 1) are important inhibitors of α_4,β_1-integrin-mediated hepatic melanoma and in a murine model of colon carcinoma metastasis, as well as potent antiadhesive properties in several cancer cell lines.[13,14] Bicyclic heterocycles **5**, containing an atropane scaffold have been found as novel inhibitors of skin cancer.[15] Spiroxindoles **6** increased the mortality of zebrafish embryos,[16] whilst molecules **7** with benzopyran skeleton were successfully tested as antimycobacterials against M. tuberculosis H37Rv strain. 4-Nitroprolines *exo*-**8**, and *endo*-**8** have been recently used as chiral organocatalysts in aldol reactions.[17] Michael-type addition of ketones to nitroalkenes was successfully organocatalyzed by *exo*-**8b** (X=H),[18] providing good to excellent diastereoselections and high enantiomeric ratios. A series of enantiopure tetrasubstituted nitroprolinate surrogates has been designed as scaffolds for proteasome inhibitors with high medicinal prospects.[19] In addition, the NH-D-EhuPhos ligand **9** has been efficiently employed in the 1,3-dipolar cycloadditions (1,3-DC) to yield nitroprolines and structurally rigid spirocompounds from chiral γ-lactams.[17,20,21] A family of enantiomerically enriched spironitroprolinates **10** were obtained by our group from imino lactones and nitroalkenes which are currently tested as anticancer agents.[22]
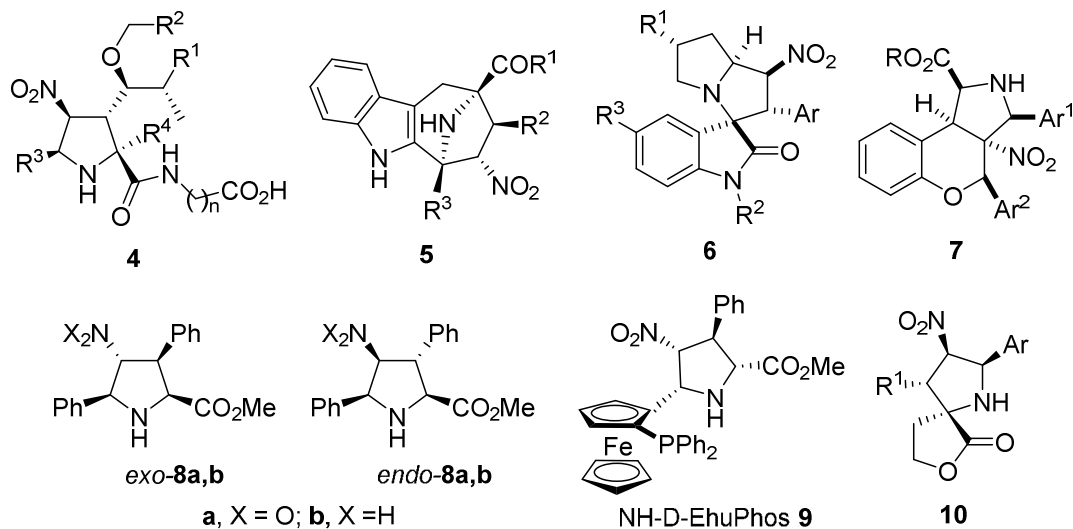
Figure 1. Interesting nitroprolinates with biological properties and with useful synthetic applications.

Continuing with our interest in the enantioselective synthesis of nitroprolinates and their synthetic applications, we described here the periselectivity exihibited by enantiopure nitroprolinates towards 1,3-DC or AAD processes in the reaction with α,β-unsaturated aldehydes and electrophilic alkenes.

RESULTS AND DISCUSSION

During initial studies of the multicomponent 1,3-DC involving enantioenriched nitroprolinates *exo*-**1a,** prepared from methyl benzylideneglycinate and β-nitrostyrene, in the presence of a chiral phosphoramidite·AgOBz complex (5 mol%) in >99:1 er (>99:1 *exo:endo* dr),[23,24] with α,β-unsaturated aldehydes and dipolarophiles, using a conventional iminium route, we detected the formation of different final products depending on the structure of the α,β-unsaturated aldehyde. Thus, in the absence of hydrogens at the γ-position of the aldehyde (*e.g.* cinnamaldehyde) the expected pyrrolizidine **2a** was formed (as a 73:27 *endo:exo* mixture of diastereoisomers in 96%

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yield) employing *N*-methylmaleimide (NMM) as dipolarophile and silver acetate (5 mol%) as catalyst (Scheme 2, eq a, and Table 1, entry 1). However, crotonaldehyde, which incorporates hydrogen atoms at the γ-position, afforded product **3a** (>99:1 dr in 94% yield) acting NMM as dienophile (Scheme 2, eq b). In this last case, an amine (instead of amide)-aldehyde-dienophile (AAD) multicomponent process took place through the intermediate 1-pyrrolidine-1,3-diene formed by a previous isomerization of the iminium ion.[25] Apart from amides, a few examples of AAD using pyrrolidine, morpholine, proline derivatives[26,27] or diallylamine[27] have been reported. In the last case only nitrostyrenes were used as dienophiles.[27]
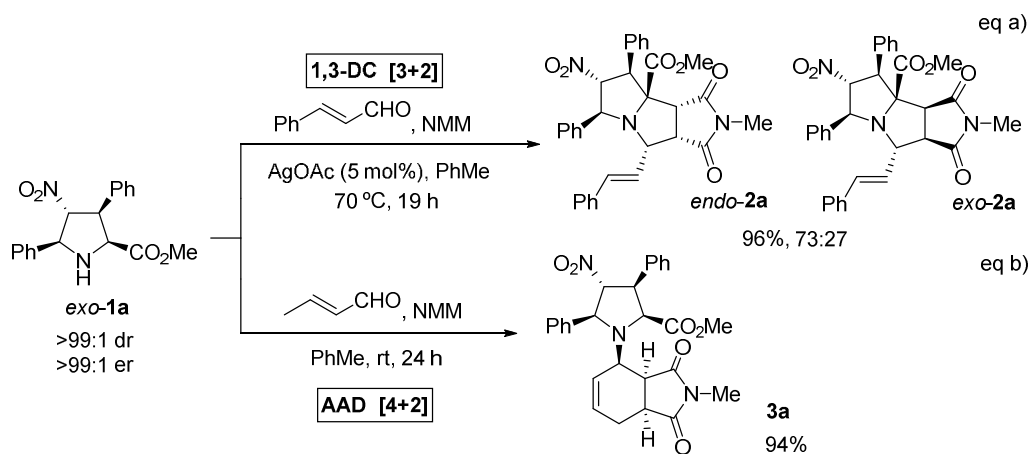
Scheme 2. Divergent multicomponent synthesis of pyrrolizidines *endo*- and *exo*-**2a** *via* 1,3-DC or polysubstituted cyclohexenes **3a** *via* AAD process from prolinate *exo*-**1a**, aldehydes and NMM.

To study the scope of the 1,3-DC, cinnamaldehyde was selected as aldehyde, for the reaction with prolinate *exo*-**1a** and different dipolarophiles at 70 °C in the presence of AgOAc (5 mol%) generating enantiomerically enriched pyrrolizidines **2a-h** in good chemical yields (up to 96%, Scheme 3 and Table 1, entries 1-8). Apart from NMM, maleimide was a suitable dipolarophile in this reaction affording a 68:32 *endo*-**2b**:*exo*-

2b mixture in combined excellent yield (95%) (Table 1, entry 2). A very high regioselectivity and *endo*-diastereoselectivity were observed in the case of the 1,3-DC performed with methyl acrylate obtaining *endo*-**2d** in 88% yield (Table 1, entry 4). Methyl fumarate furnished a 65:35 mixture of *endo*/*exo* adducts in 74% yield, the corresponding *endo*-cycloadducts **2e** being the major diastereoisomer (Table 1, entry 5). In the specific reaction with dialkyl acetylenedicarboxylates large quantities of 1,4-addition products of the nitroprolinate onto the electron-deficient alkyne were observed furnishing the desired **2f** or **2g** products as unique diastereoisomers in modest yields (Table 1, entries 6 and 7).

β-Phenylcinnamaldehyde was also tested as generator of the iminium salt in the presence of *N*-phenylmaleimide (NPM). *endo*-Cycloadduct **2h** was isolated in moderate yield as 74:26 dr (Table 1, entry 8). This result contrasted with the major *exo*-selectivity (26:74 or 32:68) detected for the reaction of the same NPM with cinnamaldehyde and both nitroprolinate *exo*-**1a** or *exo*-**1b**, respectively (Table 1, entries 3 and 9). This unexpected and exceptional behavior of NPM will be discussed later.

Relative configurations of these molecules were determined in the basis of ^{1}H NMR data and from nOe experiments and also by comparison with similar enantioenriched cycloadducts previously reported.**6** The diastereomeric ratios observed in the crude mixtures (determined by ^{1}H NMR analysis) were very similar to those obtained after separation of both diastereoisomers, which could be separated by flash chromatography (see, experimental section). Besides, these assignments are in perfect agreement with the absolute configuration revealed by X-ray diffraction analysis of molecule *endo*-**2a**[28] (see, supporting information and Scheme 3).

The reactions performed with aliphatic or aromatic aldehydes instead of using α,β-unsaturated aldehydes, gave poor conversions of the expected pyrrolidines. The
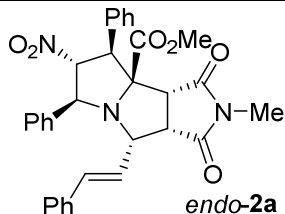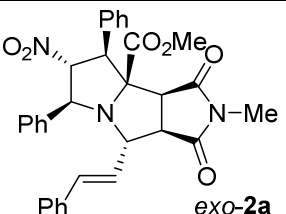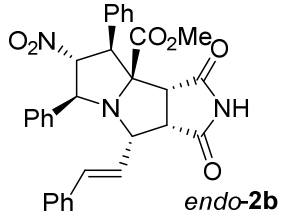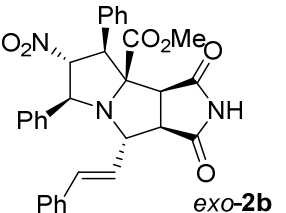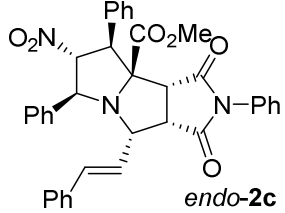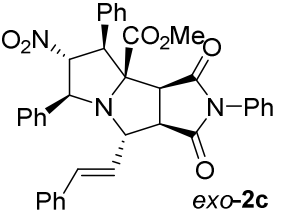
employment of dipolarophiles such as nitroalkenes, vinyl sulfones, and chalcones under

these conditions was not satisfactory.
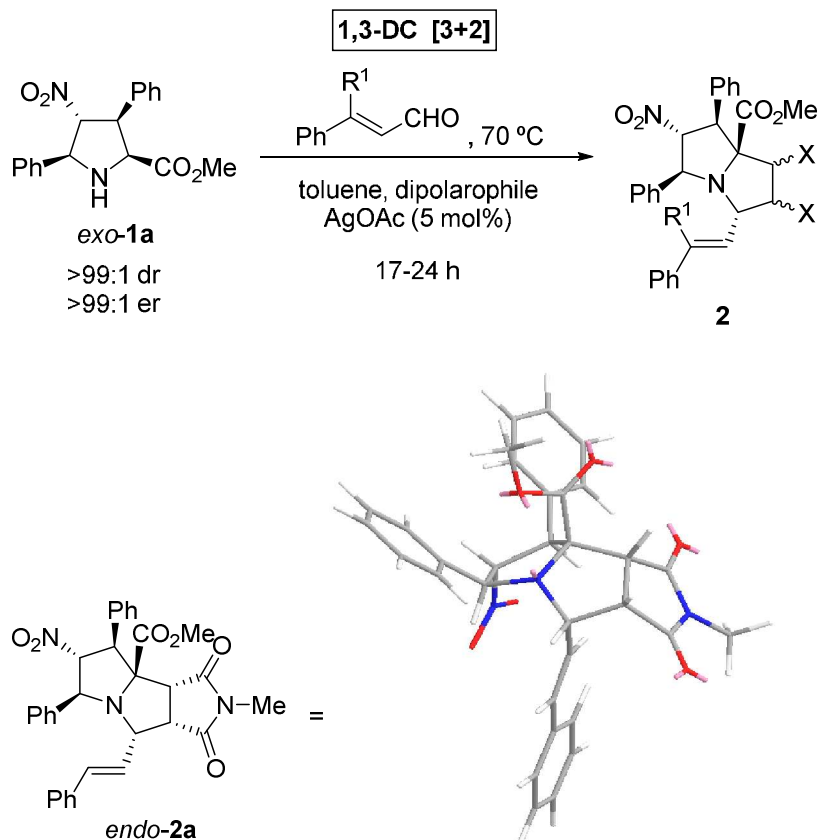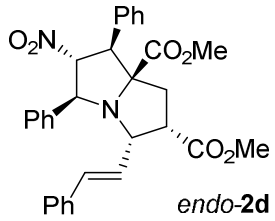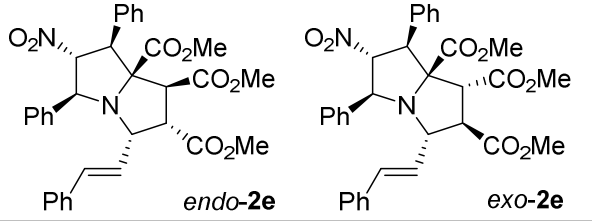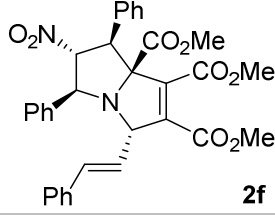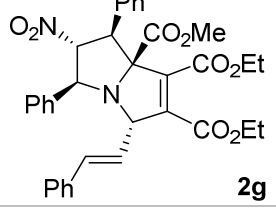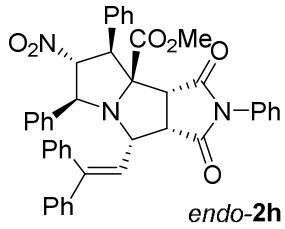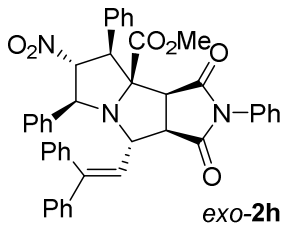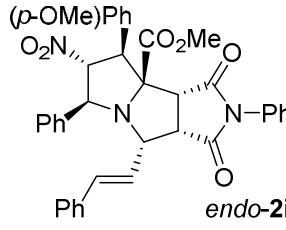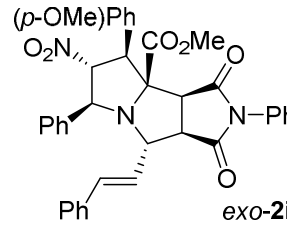
Scheme 3. Synthesis of pyrrolizidines **2** *via* 1,3-DC from prolinate *exo*-**1a**, cinnamaldehyde derivatives with different dipolarophiles and X-ray diffraction analysis of compound *endo*-**2a**.

Table 1. Synthesis of pyrrolizidines **2** *via* multicomponent 1,3-DC from enantiopure *exo*-**1a** and **1b**.

Entry	Aldehyde R^1	Dipolarophile	Product Structure and number		Conv. (%)^a	dr^a	Yield (%)^b	dr^c
1	H	NMM	*endo*-**2a**	*exo*-**2a**	>95	62:38	70, 26	73:27
2	H	Maleimide	*endo*-**2b**	*exo*-**2b**	>95	66:34	65, 30	68:32
3	H	NPM	*endo*-**2c**	*exo*-**2c**	>95	25:75	23, 67	26:74

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4	H	Methyl acrylate	*endo-***2d**		>95	96:4	88	>99:1
5	H	Dimethyl fumarate	*endo-***2e**	*exo-***2e**	>95	61:39	48, 26	65:35
6	H	DMAD[d]	**2f**		90	>99:1	31	>99:1
7	H	DEAD[e]	**2g**		90	>99:1	35	>99:1

8	Ph	NPM	endo-**2h**	exo-**2h**	90	71:29	59, 21	74:26
9[f]	H	NPM	endo-**2i**	exo-**2i**	>95	32:68	60, 28	32:68

[a] Determined by ^{1}H NMR analysis of the crude material. [b] Isolated overall yield after purification by column chromatography (silica gel, *endo, exo*). [c] Determined according to the individual yield obtained after purification. [d] Dimethyl acetylenedicarboxylate. [e] Diethyl acetylenedicarboxylate. [f] Reaction performed with nitroprolinate *exo*-**1b**.

Enantiomerically enriched *endo*-**1a** (85:15 er and >99:1 dr), obtained from the starting materials employed for the preparation of compound *exo*-**1a** but using a catalyst formed by NH-D-EhuPhos **9** and Cu(MeCN)$_4$PF$_6$,[17,20] was not so useful precursor to run this multicomponent process giving **2j** as 50/50 *endo/exo* dr, in very low yield (<20% from crude ^{1}H NMR spectra, Scheme 4). However, racemic *endo*-prolinate **1c**, obtained according to the procedure described for *exo*-**1a** and from the corresponding nitroalkene, afforded **2k** as pure racemic *endo*-stereoisomer, in 72% yield (Scheme 4). Yields represented in Scheme 4 obey to the overall yields obtained after purification as well as their corresponding dr. In the reaction of nitroprolinate *endo*-**1a**, both diastereoisomers *endo*- and *exo*-**2j** could not be separated by flash chromatography (see, experimental section).

In these examples, as well as in the described in entries 3 and 9 of Table 1, NPM approached to the dipole with an *exo*-orientation. The driving force that causes *exo* preference can be attributed to a lower destabilizing stereoelectronic interaction, mainly consisted of electrostatic repulsion between the nitro group of the dipole and the phenyl group of the dipolarophile, compared with the *endo* approach (see below in Figure 2, in the explanation of the periselectivity of these reactions). In contrast, the presence of an additional phenyl moiety of β-phenylcinnamaldehyde implies a higher Pauli repulsion in the *exo*-approach, which makes this approximation less favorable. In consequence, in this case *endo*-**2h** adduct was the major diastereoisomer obtained.
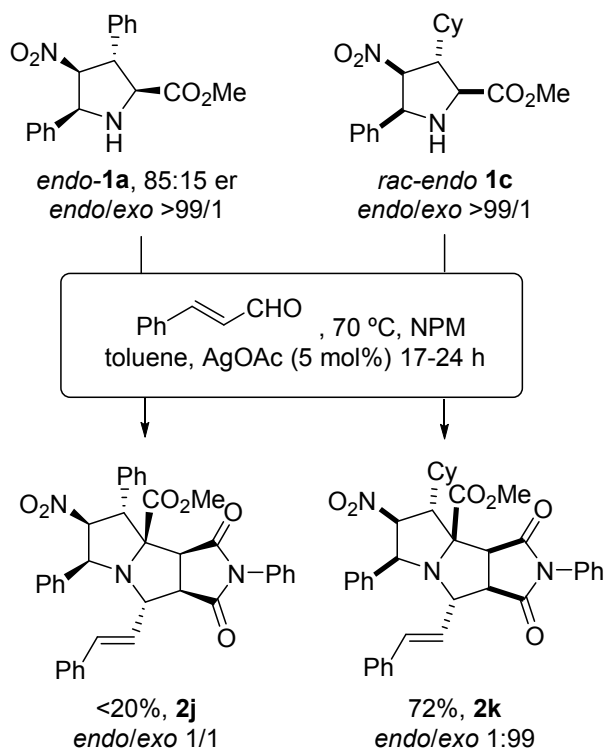
Scheme 4. Pyrrolizidines **2j** and **2k** obtained from *endo*-nitroprolinates **1** with cinnamaldehyde and NPM.

AAD reactions of compound *exo*-**1a** (>99:1 er, >99:1 dr) with crotonaldehyde and maleimides were carried out at room temperature. The reaction with NMM (2 equiv) gave compound **3a** in a very high yield (94%) and also NPM, *N*-benzylmaleimide, maleimide and maleic anhydride gave satisfactory yields (86%, 89%, 80%, and 71% respectively) of products **3b**-**3e** (Scheme 5). 1,4-Benzoquinone afforded compound **3f** in 65% yield (determined by ^{1}H NMR spectra of the crude product) at room temperature. Higher temperature (70 ºC) was needed to accomplish the reaction with 1,2-bis-(phenylsulfonyl)ethylene (BPSE) giving compound **3g** in 78% yield. Diisopropyl azodicarboxylate also promoted the multicomponent AAD reaction giving

3h in a lower yield (57%, also determined by ^{1}H NMR spectra of the crude product).

Diastereomeric compounds **3f** and **3h** could not be neither purified by column

chromatography due to partial decomposition nor recrystallized in order to obtain pure

samples to accomplish the full characterization. Next, α,β-unsaturated aldehydes with

hydrogen atoms at the γ-position such as 3-methyl-2-butenal, 2-pentenal and 2-hexenal

were appropriate aldehydes for the success of the name AAD multicomponent reaction

furnishing with NPM adducts **3i**, **3j** and **3k** in 62%, 89%, and 72%, respectively

(Scheme 5). In all these examples, aminocyclohexenes **3** were isolated as unique

diastereoisomers. However, the reaction with geranial, NPM and nitroprolinate *exo*-**1a**

gave a complex crude mixture containing the major adduct **3l** and various unidentified

compounds. After purification, only a 53% yield of the product **3l** could be isolated.

Compounds **3** were obtained in excellent dr affording enantiomerically pure

cycloadducts after flash chromatography, except compounds **3f** and **3h** as mentioned

above. In the case of the cycloadduct **3e**, derived from maleic anhydride, it was obtained

after chromatographic purification as a 63:37 mixture of diastereoisomers, the structure

of the major compound being drawn in Scheme 5. The absolute configuration of new

compound **3b** was unambiguously established by X-ray diffraction analysis[29] (see,

Supporting Information and Scheme 5). For other molecules **3** complementary ^{1}H NMR

analysis also confirmed the drawn structures depicted in Scheme 5.

3a, 94%

3b, 86%

3c, 89%

3d, 80%

3e, 71%
63:37 dr

3f, 65%

3g, 78% (70 °C)

3h, 57%

3i, 62%

3j, 89%

3k, 72%

3l, 53%
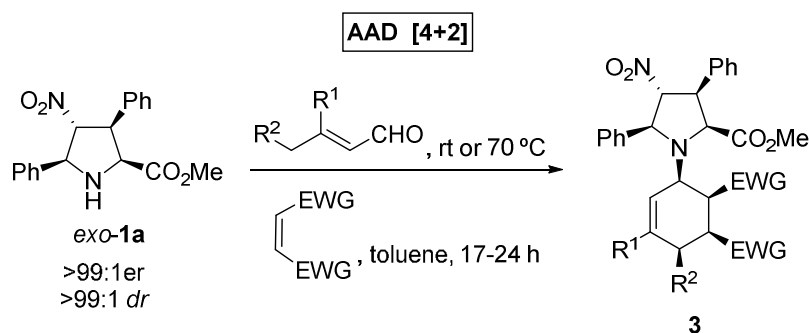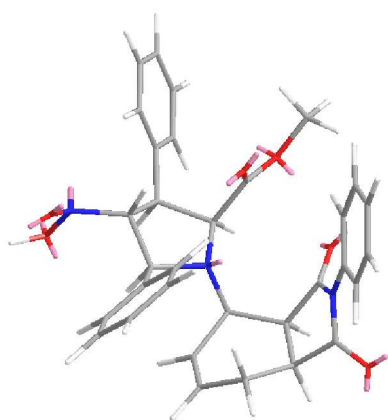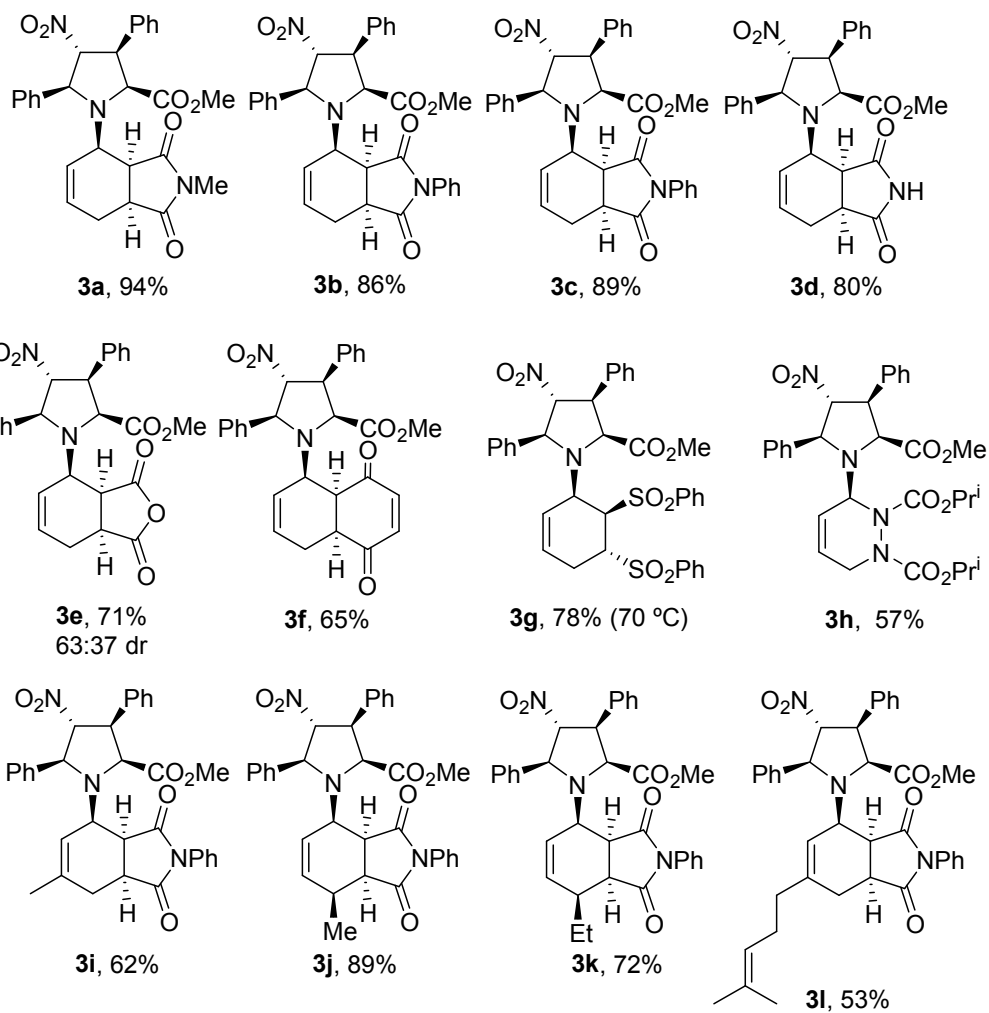
X-Ray crystal structure of **3b**

Scheme 5. Polyfunctionalized cyclohexenes **3** obtained from AAD employing nitropolinate *exo*-**1a**, α,β-unsaturated aldehydes with hydrogen atoms at the γ-position and dienophiles and X-ray diffraction analysis of compound **3b**.

Two nitroprolinates, *exo*-**1b** and *rac-endo*-**1c** were tested as precursors in this AAD domino reaction with NPM and crotonaldehyde. The reaction of the *exo*-**1b** gave **3m** in 81% yield, whereas *rac-endo*-**1c** afforded compound **3n** as a 1:1 mixture of two inseparable diastereoisomers in 79% overall yield (Scheme 6).
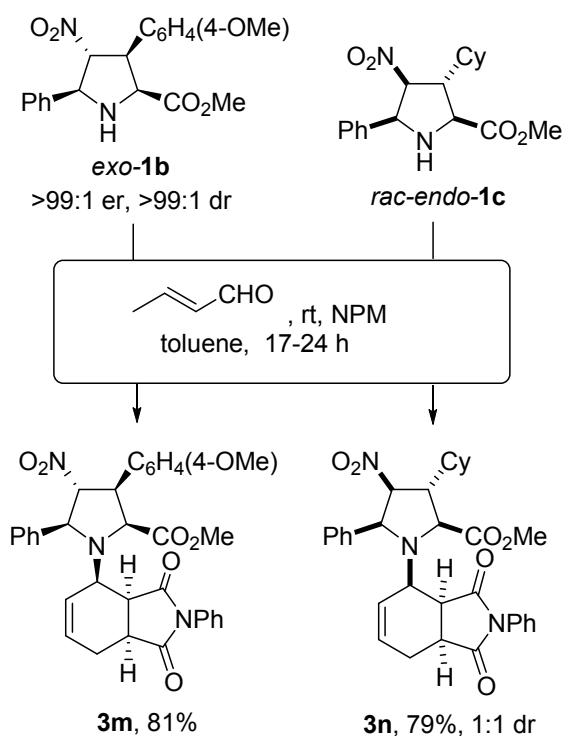
Scheme 6. Products **3m** and **3n** obtained from AAD sequence employing different *exo* and *endo*-nitroprolinates with crotonaldehyde and NPM.

Noteworthy, no AAD multicomponent reaction was observed during the reaction of L-proline methyl ester **11** or proline ester derivatives **12**, **13** and **14**. In these cases,

the 1,3-DC occurred instead and the corresponding *endo*-pyrrolizidines **15-18** were

formed in 61%, 69%, 67% and 68% yield, respectively (Scheme 7).
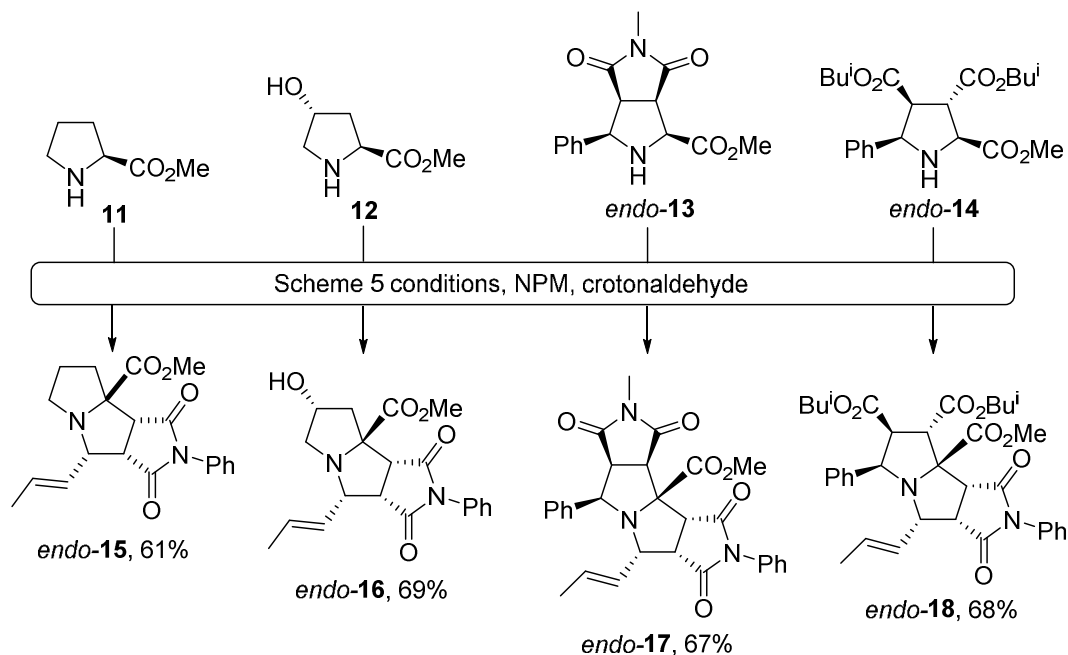
Scheme 7. Products *endo*-**15-18** obtained from 1,3-DC employing different methyl

prolinates with crotonaldehyde and NPM.

According to these described results, the presence of the nitro group is crucial in

the origin of the periselectivity in these multicomponent reactions. Thus, the effect of

the presence and absence of the nitro group in the starting prolinate derivatives *exo*-**1a,**

11, *endo*-**13** and *endo*-**14** (derived from dimethyl fumarate) in the reaction outcome was

next analyzed by means of DFT calculations. We selected the reactions of NMM,

crotonaldehyde and proline derived esters with different substitution patterns in order to

shed light on the observed periselectivity of each reactive system between the [4+2]

AAD multicomponent reaction or the pyrrolizidine synthesis *via* 1,3-DC.

The initial step in the proposed mechanism consists in the formation of the iminium cation **A**, derived from the condensation between the proline derivative and crotonaldehyde (Scheme 8). This intermediate has two acidic protons. Therefore, in presence of a base, **A** can evolve into the azomethine ylide **B** by abstraction of the hydrogen atom located in α-position of the methoxycarbonyl group, that leads to pyrrolizidines **2**, **15-18** or to a dienamine intermediate **C** by abstraction of the hydrogen atom in γ-position of crotonaldehyde, thus forming cyclohexenylpyrrolidines **3**.
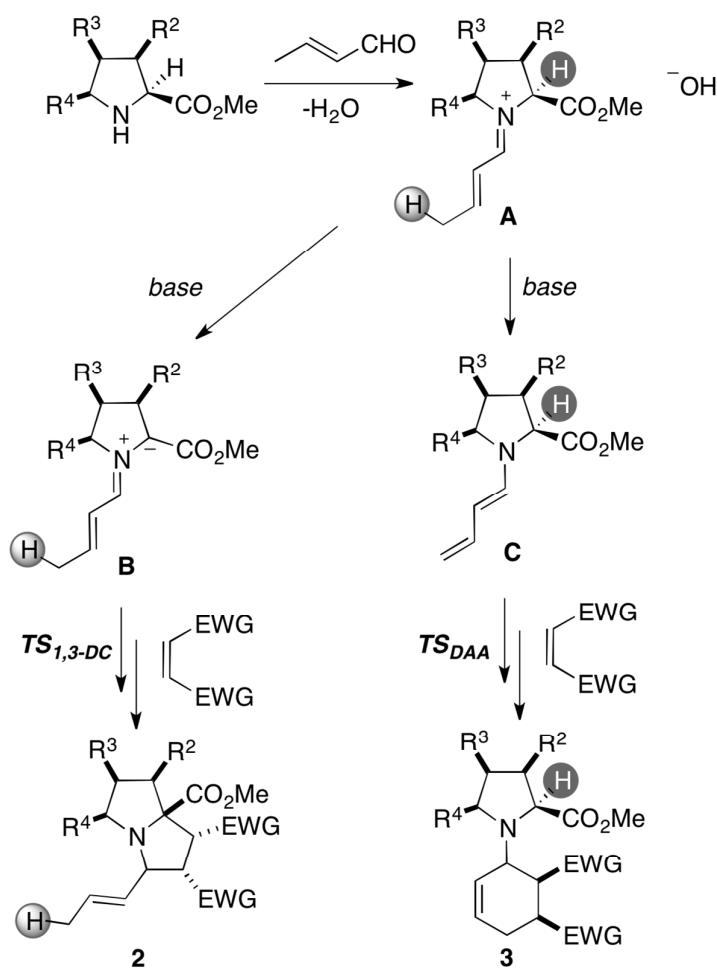
Scheme 8. General scheme of the reaction of prolinates, aldehydes and dipolarophiles affording pyrrolizidines **2** or cyclohexenylpyrrolidines **3**. Acidic positions are highlighted.

According to the Fukui frontier molecular orbital (FMO) theory,[30] $\pi 4s + \pi 2s$ cycloaddition reactions are mainly governed by symmetry allowed HOMO$_{dipole/diene}$-LUMO$_{dipolarophile/dienophile}$ interactions. Within this framework, small energy gap $\Delta E_{HOMO\text{-}LUMO}$ is related to a high reactivity. Inspection of the reagent FMOs shown that the less stable azomethine ylides **B** seem to be more reactive than dienamines **C**, regardless the proline derivative **1** used (see, Supporting Information). As a consequence of this reactivity-stability dichotomy, in which unstable reagents are the most reactive ones,[31] exploration of all the possible transition states associated with the formation of pyrrolizidines **2**, **15-18** and cyclohexenyl pyrrolidines **3** was carried out. Nevertheless, if we assume a pre-equilibrium between all the possible reactive species, Curtin-Hammet kinetics[32] show that the product ratio depends on the free Gibbs activation energy difference of the corresponding transition structures. The relative Gibbs free energies and main geometrical features of the less energetic computed transition states are shown in Figures 2-4. As far as nitroproline *exo*-**1a** is considered, our calculations show that the transition structure associated with the AAD multicomponent reaction (**TS$_{AAD}$**-*exo*-**1a**) is 1.2 kcal mol^{-1} more stable than its 1,3-DC analog **TS$_{1,3\text{-}DC}$**-*exo*-**1a** (Figure 2). Therefore, cyclohexenylpyrrolidines **3** will be preferentially formed in this case, despite the higher reactivity of dipole **B**. The computed energetic difference between all the possible transition structures **TS$_{AAD}$** associated with formation of cyclohexenylpyrrolidines **3** (especially those comparing the *endo*- and the *exo*-

approach) show a theoretical dr of *c.a.* 99:1, in perfect agreement with the experimental results (see, Supporting Information).

Analysis of the geometries depicted in Figure 2 also supports a diastereofacial bias in highly substituted nitroproline *exo*-**1a** derived transition state, where substituents in position 2, 3 and 5 effectively block one face of the azomethine ylide or the aminodiene intermediate. Therefore, in **TS$_{1,3-DC}$-*exo*-1a** the dipolarophile has to approach towards the dipole by the nitro group face. Within this approach, high Pauli repulsions between the dipolarophile and the nitro group are expected (Figure 2). These stereoelectronic effects are reflected in the high energy required to deform the azomethine ylide **B** from its relaxed geometry to the one that adopts in the transition state structure, making the 1,3-DC energetically inaccessible, and thus converting the low-distorted AAD reaction the preferred one (see the distortion/interaction analysis[33] in the Supporting Information). Regarding these Pauli repulsions, is it plausible to assume that they are the responsible of the favorable *exo*-approach of NPM in the course of 1,3-DCs.

Figure 2. Relative Energies, Gibbs free energy (between parenthesis) and main geometrical features of the most stable transition structures associated with the 1,3-DC (**TS$_{1,3\text{-DC}}$-*exo*-1a**) or multicomponent AAD (**TS$_{ADD}$-*exo*-1a**) associated with the reaction of crotonaldehyde, NMM and *exo*-**1a** (A) computed at B3LYP/6-31G* level of theory and M06-2X/6-31G*//B3LYP/6-31G* level of theory (in italics and between brackets, respectively) at 298K. Distances and energies are in Å and in kcal mol-1, respectively.

On the other hand, the employment of proline derivatives **11** (Scheme 7) implies a change in the periselectivity of the reaction. In this example, preferential formation of pyrrolizidine **15** was observed, being **TS$_{1,3\text{-DC}}$** (associated with the 1,3-DC) *c.a.* 3 kcal mol^{-1} more stable than their **TS$_{AAD}$** counterpart, in good agreement with the

periselectivity observed experimentally (Figure 3). A detailed inspection of the geometries shows that generation of reactive azomethine ylides **B** (Scheme 8) forces the pyrrolidine ring (and in consequence the iminium ion **A**) into a planar conformation in which all substituents are placed in an isoclinal position. Within this fixed conformation, the substituents can effectively block one or both faces of the azomethine ylide. Therefore, it was observed that an small additional energy is required for the deformation of the azomethine ylide during an *endo*-approach, increasing the activation barrier associated with the 1,3-DC. But never this increment generates a **TS$_{1,3\text{-DC}}$** with higher energy than the corresponding **TS$_{AAD}$** one (14.4 kcal mol^{-1} and 18.7 kcal mol^{-1}, respectively). Thus, a strong preference for the 1,3-DC is observed.

TS$_{1,3\text{-DC}}$-11
0.0 (0.0)
[0.0 (0.0)]

TS$_{AAD}$-11
+2.6 (+1.8)
[+3.8 (+3.0)]

ΔΔE$_a$ (ΔΔG$_a$): B3LYP
[ΔΔE$_a$ (ΔΔG$_a$): M06-2X/B3LYP]

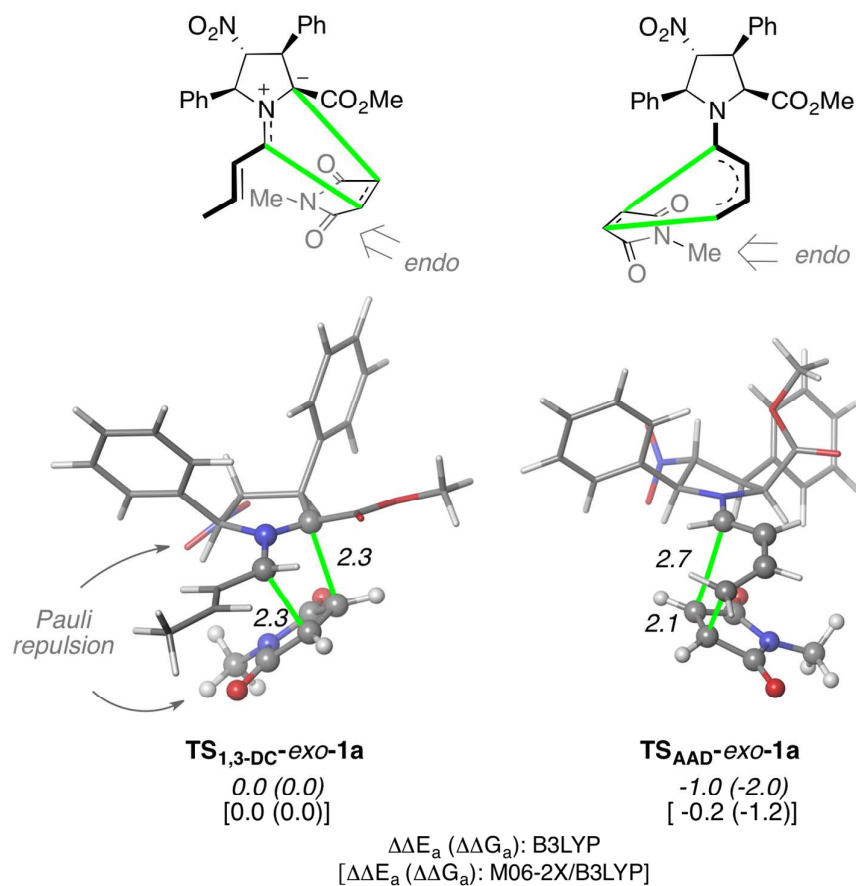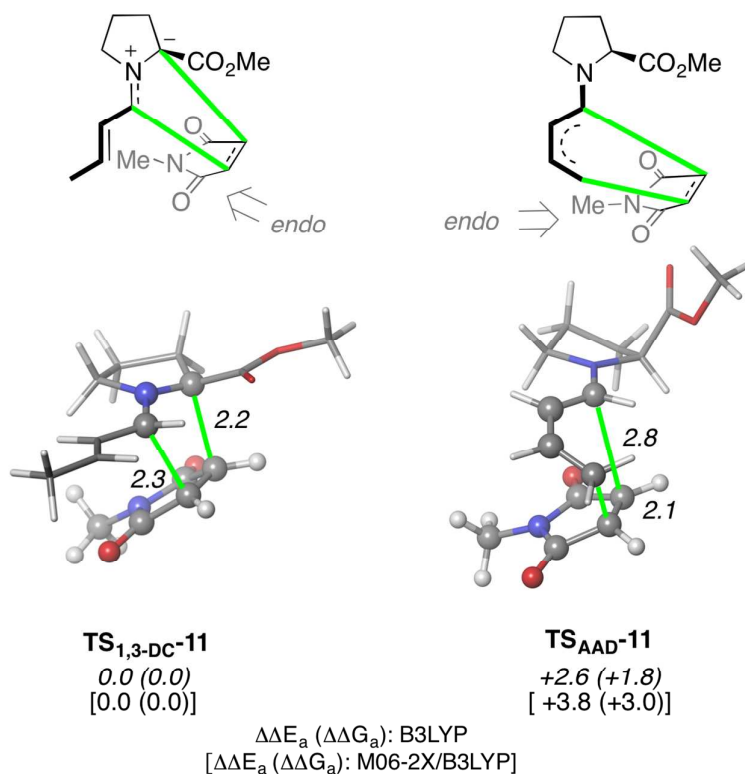**Figure 3.** Relative Gibbs free energy and main geometrical features of the most stable transition structures associated with the 1,3-DC (**TS$_{1,3\text{-DC}}$-11**) or multicomponent AAD (**TS$_{AAD}$-11**) associated with the reaction of crotonaldehyde, NMM and (B) proline **11**. See caption of Figure 2 for further details.

However, in dienamine intermediates (Figure 4, *A* and *B*) the pyrrolidine ring has a twist conformation where most of the substituents are placed in an equatorial position. In these both examples, the steric hindrance is considerably lower than in the former **TS$_{AAD}$-11**, and therefore, the activation barrier is less influenced by the substituents (Figure 4).

For the maleimide derivative *endo*-**13**, the *cis*-substitution pattern in the pyrrolidine ring leads to the effective blockage of only one of the prochiral faces, and low distortion of the initial reagent is required for the attack to the less hindered face. Therefore, in this case, 1,3-DC was preferred over multicomponent AAD process such as it was observed for L-proline methyl ester **11**. In consequence, formation of pyrrolizidine **17** is theoretically expected. In the case of fumaric ester derivative **14**, despite having a *trans*-substitution pattern that should block both prochiral faces of azomethine ylide in a similar way to *exo*-**1a**, the steric requirements of the methoxycarbonyl groups are smaller than phenyl or nitro substituents, and the energy required to distort the initial azomethine ylide is lower. In fact, the transition structure associated with the 1,3-DC (**TS$_{1,3\text{-DC}}$-*endo*-14**) was found to be 3.6 kcal mol^{-1} more stable than that of its AAD counterpart (**TS$_{AAD}$-*endo*-14**). Preferential formation of pyrrolizidines **15**-**18** are theoretically assessed when **11**-**14** are used as starting materials.

A

TS$_{1,3\text{-DC}}$-*endo*-13
0.0 (0.0)
[0.0 (0.0)]

TS$_{AAD}$-*endo*-13
+3.0 (+2.6)
[+2.6 (+2.1)]

B

TS$_{1,3\text{-DC}}$-*endo*-14
0.0 (0.0)
[0.0 (0.0)]

TS$_{AAD}$-*endo*-14
+2.0 (+0.5)
[+5.0 (+3.6)]

$\Delta\Delta E_a$ ($\Delta\Delta G_a$): B3LYP
[$\Delta\Delta E_a$ ($\Delta\Delta G_a$): M06-2X/B3LYP]
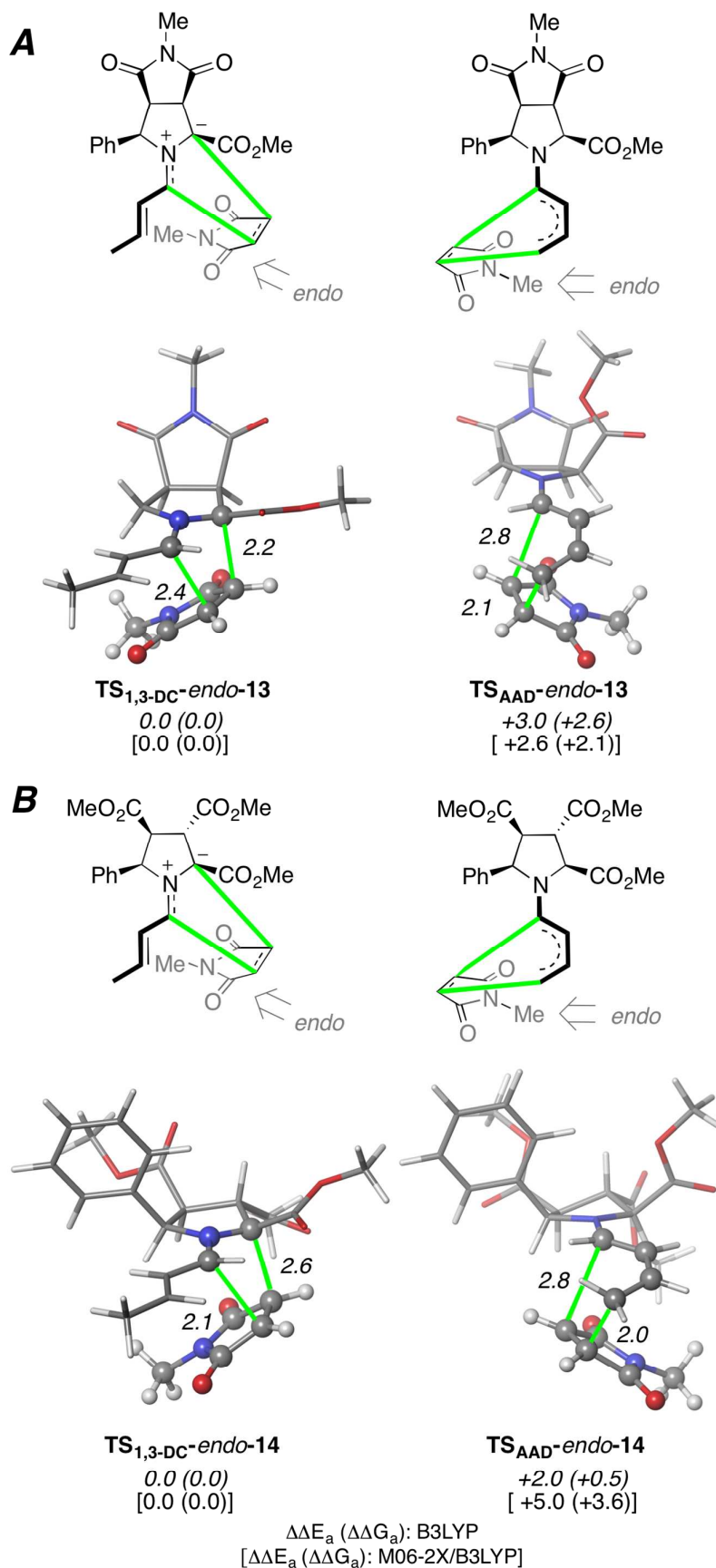
Figure 4. Relative Gibbs free energy and main geometrical features of the most stable transition structures associated with the 1,3-DC (**TS$_{1,3\text{-DC}}$-*endo*-13** and **TS$_{1,3\text{-DC}}$-*endo*-14**) or multicomponent AAD (**TS$_{AAD}$-*endo*-13** and **TS$_{AAD}$-*endo*-14**) associated with the reaction of crotonaldehyde, NMM and (A) *endo*-**13**, or (B) *endo*-**14**. See caption of Figure 2 for further details.

CONCLUSION

An example of total periselectivity has been demonstrated in the multicomponent 1,3-DC or AAD of enantiopure methyl *exo-* or *endo*-4-nitroprolinates in the presence of a dipolarophile and an α,β-unsaturated aldehyde. The crucial presence of a nitro group in the heterocycle and the existence or not of hydrogen atoms at the γ-position of the aldehyde determines the periselectivity towards AAD or 1,3-DC, respectively. The diastereomeric control was notable in the [3+2] process and excellent in [4+2] cycloadditions affording in this last case enantiopure polysubstituted 3-aminocyclohexenes. On the basis of the DFT calculations here presented, it was supported that azomethine ylides derived from proline derivatives and crotonaldehyde are in general more reactive than its dienamine counterparts, being the 1,3-DC preferred over the AAD reaction. Only in the case of highly hindered azomethine ylides, such as the one derived from *exo*-**1a**, 1,3-DC is hindered due to the huge energy required to distort the reagents into the transition structure geometry. Therefore, the less reactive dienamine takes importance, being the AAD pathway the only one energetically

accessible. The evaluation of all these series of molecules as anticancer agents are currently underway.

EXPERIMENTAL SECTION

General Experimental Methods: All commercially available reagents and solvents were used without further purification, only aldehydes were also distilled prior to use. Analytical TLC was performed on Schleicher & Schuell F1400/LS 254 silica gel plates, and the spots were visualised under UV light (λ = 254 nm). Flash chromatography was carried out on handpacked columns of Merck silica gel 60 (0.040-0.063 mm). Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer 341 polarimeter with a thermally jacketted 5 cm cell at approximately 25 ºC and concentrations (*c*) are given in g/100 mL. The structurally most important peaks of the IR spectra (recorded using a Nicolet 510 P-FT) are listed and wavenumbers are given in cm^{-1}. NMR spectra were obtained using a Bruker AC-300 or AC-400 and were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR, using CDCl$_3$ as solvent and TMS as internal standard (0.00 ppm). The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved and br s = broad signal. All coupling constants (*J*) are given in Hz and chemical shifts in ppm. ^{13}C NMR spectra were referenced to CDCl$_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, CH$_2$ and CH$_3$. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV using a Shimadzu QP-5000 by injection or DIP; fragment ions in *m/z* are given with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were measured on

an instrument using a quadrupole time-of-flight mass spectrometer (QTOF) and also through the electron impact mode (EI) at 70 eV using a Finnigan VG Platform or a Finnigan MAT 95S.

Computational methods: All the computational mechanistic studies were carried out with the Gaussian09 [34] suite of programs. Density functional Theory (DFT) geometry optimizations and harmonic analysis were preformed with the B3LYP [35] functional. Relative energies were computed by means of single-point calculations on the optimized geometries with the M06-2X[36] functional.

This latter functional was chosen because it is well suited for the treatment of nonbonding interactions and dispersion forces in densely substituted interacting systems[37] and produce similar geometries to B3LYP, [38] although it tends to slightly overestimate the barriers of hetero Diels Alder reactions. [39]

The 6-31G* basis set was used. Solvent effects were computed with the PCM method using toluene as solvent.[40] All the stationary points were characterized by harmonic analysis. Reactants, intermediates and products showed positive definite Hessian values. Transition structures (TSs) showed one and only one imaginary frequency associated with nuclear motion along the chemical transformation. Activation and reaction (Gibbs) energies were calculated at 298.15 K. Figures including optimized structures were made with Maestro[41] and CYL-view[42] programs. Orbital diagrams were prepared by using the Gauss-view interface. [43]

General procedure for the synthesis of pyrrolizidines 2a-2k: To a stirred solution of the nitroprolinate **1** (0.1 mmol) in toluene (1 mL) the aldehyde (0.1 mmol) and the dipolarophile (0.1 mmol) were added. Then a 5 mol% of AgOAc (0.005 mmol, 0.84

mg) was added and the reaction was stirred overnight at 70 °C in the dark. Then the reaction was filtered through a celite path and the solvent was evaporated under reduced pressure. The crude mixture was purified by flash column chromatography over silica gel (20% EtOAc in hexane as the eluent) to furnish the corresponding product **2**.

Methyl (3aS,4S,6S,7R,8R,8aR,8bR)-2-methyl-7-nitro-1,3-dioxo-6,8-diphenyl-4-((E)-styryl)octahydropyrrolo[3,4-a]pyrrolizine-8a(6H)-carboxylate (endo-2a): The representative procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg), cinnamaldehyde (0.1 mmol, 12.6 μL) and *N*-methylmaleimide (0.1 mmol, 11.1 mg). The desired product was obtained as colorless prisms (38.6 mg, 70% yield), mp 194-197 °C (Et$_2$O), $[\alpha]_D^{28}$ = +160.3 (*c* 1.0, CHCl$_3$), IR (neat) ν_{max}: 1742, 1697, 1552, 1208, 1037, 968 cm^{-1}. ^{1}H NMR δ: 3.19 (s, 3H), 3.30 (s, 3H), 3.53 (t, *J* = 8.0 Hz, 1H), 4.20 (dd, *J* = 10.2, 8.0 Hz, 1H), 4.34 (d, *J* = 8.0 Hz, 1H), 4.69 (d, *J* = 8.4 Hz, 1H), 4.86 (d, *J* = 9.9 Hz, 1H), 5.41 (dd, *J* = 9.9, 8.4 Hz, 1H), 5.89 (dd, *J* = 15.5, 10.2 Hz, 1H), 6.31 (d, *J* = 15.5 Hz, 1H), 6.82-6.91 (m, 2H), 7.13-7.49 (m, 13H). ^{13}C NMR δ: 25.6, 52.0, 52.1, 52.7, 52.8, 64.9, 67.9, 82.7, 96.7, 122.6, 126.7, 126.9, 128.1, 128.3, 128.4, 128.8, 128.9, 129.0, 134.8, 135.8, 136.0, 139.0, 171.4, 175.6, 176.8. MS (EI) *m/z*: 551 (M$^+$, <1%), 505 (41), 492 (59), 446 (32), 445 (100), 256 (29), 193 (61), 115 (58), 91 (25). HRMS calculated for C$_{32}$H$_{29}$N$_3$O$_6$: 551.2056; found: 551.2057.

Methyl (3aR,4S,6S,7R,8R,8aR,8bS)-2-methyl-7-nitro-1,3-dioxo-6,8-diphenyl-4-[(E)-styryl]octahydropyrrolo[3,4-a]pyrrolizine-8a(6H)-carboxylate (exo-2a): This minor product was obtained as colorless plates (14 mg, 26% yield), mp 88-90 °C (Et$_2$O), $[\alpha]_D^{29}$ = +76.1 (*c* 0.5, CHCl$_3$), IR (neat) ν_{max}: 1737, 1700, 1551, 1434, 1372, 1279, 1131, 1084, 968 cm^{-1}. ^{1}H NMR δ: 3.04 (s, 3H), 3.23 (s, 3H), 3.82 (dd, *J* = 9.9, 6.6 Hz, 1H), 4.15 (d, *J* = 9.9 Hz, 1H), 4.48 (dd, *J* = 7.9, 6.6 Hz, 1H), 4.56 (d, *J* = 8.9 Hz, 1H), 4.83 (d, *J* = 7.6 Hz, 1H), 5.44 (dd, *J* = 8.9, 7.6 Hz, 1H), 5.90 (dd, *J* = 15.7, 7.9 Hz, 1H), 6.53

(d, J = 15.7 Hz, 1H), 6.83-6.99 (m, 2H), 7.12-7.50 (m, 13H). ^{13}C NMR δ: 25.3, 52.3, 53.0, 56.0, 58.0, 65.7, 68.2, 82.9, 97.3, 125.4, 126.7, 127.2, 128.1, 128.2, 128.5, 128.8, 129.0, 129.2, 134.8, 135.5, 135.8, 139.4, 169.2, 174.5, 175.8. MS (EI) *m/z*: 551 (M$^+$, <1%), 506 (19), 505 (55), 492 (18), 446 (17), 445 (48), 256 (19), 194 (18), 193 (100), 115 (57), 91 (21). HRMS calculated for $C_{32}H_{29}N_2O_4$ [M–NO$_2$]: 505.2127; found: 505.2129.

Methyl   (3aS,4S,6S,7R,8R,8aR,8bR)-7-nitro-1,3-dioxo-6,8-diphenyl-4-[(E)-styryl]octahydropyrrolo[3,4-a]pyrrolizine-8a(6H)-carboxylate   (endo-2b): The representative procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg), cinnamaldehyde (0.1 mmol, 12.6 μL) and maleimide (0.1 mmol, 9.7 mg). The desired product was obtained as pale pink prisms (35.0 mg, 65% yield), mp 249-252 ºC (Et$_2$O), $[\alpha]_D^{26}$ = +179.2 (*c* 1.0, CHCl$_3$), IR (neat) ν_{max}: 1711, 1554, 1356, 1192, 750 cm^{-1}. ^{1}H NMR δ: 3.33 (s, 3H), 3.57 (t, J = 8.3 Hz, 1H), 4.21 (dd, J = 10.3, 8.5 Hz, 1H), 4.37 (d, J = 8.2 Hz, 1H), 4.91 (d, J = 8.4 Hz, 1H), 5.01 (d, J = 10.2 Hz, 1H), 5.50 (dd, J = 10.2, 8.4 Hz, 1H), 5.93 (dd, J = 15.4, 10.3 Hz, 1H), 6.28 (d, J = 15.4 Hz, 1H), 6.84-6.91 (m, 2H), 7.10-7.50 (m, 13H), 8.67 (br s, 1H). ^{13}C NMR δ: 51.7, 52.8, 52.9, 54.0, 64.4, 67.6, 82.5, 96.3, 122.4, 126.7, 126.9, 128.1, 128.2, 128.3, 128.4, 128.8, 128.9, 129.0, 134.3, 135.9, 136.1, 138.8, 171.4, 175.3, 176.9. MS (EI) *m/z*: 538 (M$^+$, <1%), 491 (39), 479 (19), 478 (58), 440 (15), 432 (34), 431 (100), 256 (31), 193 (65), 191 (19), 178 (15), 157 (18), 141 (16), 128 (15), 115 (70), 91 (28). HRMS calculated for $C_{31}H_{27}N_2O_4$ [M–NO$_2$]: 491.1971; found: 491.1963.

Methyl   (3aR,4S,6S,7R,8R,8aR,8bS)-7-nitro-1,3-dioxo-6,8-diphenyl-4-[(E)-styryl]octahydropyrrolo[3,4-a]pyrrolizine-8a(6H)-carboxylate (exo-2b): This minor product was obtained as yellow prisms (16.2 mg, 30% yield), mp 108-111 ºC (Et$_2$O), $[\alpha]_D^{26}$ = +81.3 (*c* 1.0, CHCl$_3$), IR (neat) ν_{max}: 1712, 1552, 1340, 1180, 737 cm^{-1}. ^{1}H

NMR δ: 3.27 (s, 3H), 3.83 (dd, J = 9.9, 7.6 Hz, 1H), 4.14 (d, J = 9.9 Hz, 1H), 4.51 (d, J = 8.6 Hz, 1H), 4.50-4.56 (m, 1H), 4.76 (d, J = 7.7 Hz, 1H), 5.37 (dd, J = 8.6, 7.7 Hz, 1H), 5.84 (dd, J = 15.7, 7.7 Hz, 1H), 6.51 (d, J = 15.7 Hz, 1H), 6.81-6.92 (m, 2H), 7.11-7.46 (m, 13H), 8.36 (br s, 1H). ^{13}C NMR δ: 52.3, 53.5, 57.3, 57.8, 65.9, 68.4, 83.0, 97.2, 125.1, 126.7, 126.8, 127.3, 128.1, 128.2, 128.3, 128.4, 128.5, 128.8, 129.0, 129.2, 134.6, 135.8, 139.2, 169.1, 174.2, 175.9. MS (EI) m/z: 538 (M$^+$, <1%), 492 (17), 491 (49), 431 (34), 256 (15), 194 (18), 193 (100), 191 (12), 115 (52), 91 (18). HRMS calculated for $C_{31}H_{27}N_2O_4$ [M–NO$_2$]: 491.1971; found: 491.1968.

Methyl (3aS,4S,6S,7R,8R,8aR,8bR)-7-nitro-1,3-dioxo-2,6,8-triphenyl-4-[(E)-styryl]octahydropyrrolo[3,4-a]pyrrolizine-8a(6H)-carboxylate *(exo-2c):* The representative procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg), cinnamaldehyde (0.1 mmol, 12.6 μL) and *N*-phenylmaleimide (0.1 mmol, 17.3 mg). The desired product was obtained as colorless prisms (40.9 mg, 67% yield), mp 161-164 ºC (Et$_2$O), $[\alpha]_D^{24}$ = -31.5 (c 0.6, CHCl$_3$), IR (neat) ν_{max}: 1707, 1552, 1387, 1192, 742 cm^{-1}. ^{1}H NMR δ: 3.25 (s, 3H), 3.94 (dd, J = 10.1, 6.6 Hz, 1H), 4.22 (d, J = 10.1 Hz, 1H), 4.51-4.70 (m, 2H), 4.88 (d, J = 7.7 Hz, 1H), 5.47 (dd, J = 9.0, 7.7 Hz, 1H), 5.92 (dd, J = 15.7, 8.0 Hz, 1H), 6.54 (d, J = 15.7 Hz, 1H), 6.83-6.97 (m, 2H), 7.12-7.51 (m, 18H). ^{13}C NMR δ: 52.4, 53.1, 55.9, 57.9, 65.9, 68.3, 83.3, 97.1, 125.3, 126.5, 126.7, 127.2, 128.1, 128.2, 128.5, 128.7, 128.8, 129.0, 129.2, 129.3, 132.1, 134.8, 135.3, 135.9, 139.3, 169.3, 173.4, 174.9. MS (EI) m/z: 613 (M$^+$, <1%), 568 (18), 567 (44), 507 (23), 440 (10), 394 (11), 256 (15), 193 (100), 115 (48), 91 (19). HRMS calculated for $C_{37}H_{31}N_2O_4$ [M–NO$_2$]: 567.2284; found: 567.2277.

Methyl (3aS,4S,6S,7R,8R,8aR,8bR)-7-nitro-1,3-dioxo-2,6,8-triphenyl-4-[(E)-styryl]octahydropyrrolo[3,4-a]pyrrolizine-8a(6H)-carboxylate (endo-2c): This minor product was obtained as colorless prisms (14.3 mg, 23% yield), mp 209-212 ºC (Et$_2$O),

$[\alpha]_D^{26}$ = -131.2 (*c* 1.0, CHCl$_3$), IR (neat) ν_{max}: 1707, 1549, 1379, 1184, 739 cm^{-1}. ^{1}H

NMR δ: 3.36 (s, 3H), 3.72 (t, *J* = 8.1 Hz, 1H), 4.27 (dd, *J* = 10.3, 7.9 Hz, 1H), 4.58 (d, *J*

= 8.2 Hz, 1H), 4.86 (d, *J* = 8.6 Hz, 1H), 5.01 (d, *J* = 10.6 Hz, 1H), 5.55 (dd, *J* = 10.6,

8.6 Hz, 1H), 6.01 (dd, *J* = 15.4, 10.3 Hz, 1H), 6.35 (d, *J* = 15.4 Hz, 1H), 6.86-6.93 (m,

2H), 7.11-7.58 (m, 18H). ^{13}C NMR δ: 51.9, 52.2, 53.0, 53.1, 65.1, 68.3, 82.9, 96.2,

122.5, 126.6, 126.7, 127.0, 128.2, 128.3, 128.4, 128.8, 128.9, 129.0, 129.3, 129.6,

131.7, 134.0, 135.9, 138.5, 171.4, 174.4, 175.8. MS (EI) m/z: 613 (M+, <1%), 568 (16),

567 (36), 555 (24), 554 (61), 508 (40), 507 (100), 440 (36), 394 (22), 256 (44), 219

(18), 194 (20), 193 (97), 191 (26), 178 (20), 157 (19), 141 (25), 115 (94), 91 (40).

HRMS calculated for C$_{37}$H$_{31}$N$_2$O$_4$ [M–NO$_2$]: 567.2284; found: 567.2278.

Dimethyl   (2S,3S,5S,6R,7R,7aS)-6-nitro-5,7-diphenyl-3-[(E)-styryl]tetrahydro-

1H-pyrrolizine-2,7a(5H)-dicarboxylate (endo-2d): The representative procedure was

followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg), cinnamaldehyde (0.1

mmol, 12.6 μL) and methyl acrylate (0.1 mmol, 22.6 μL). The desired product was

obtained as sticky yellow oil (46.4 mg, 88% yield), $[\alpha]_D^{26}$ = +40.2 (*c* 1.5, CHCl$_3$), IR

(neat) ν_{max}: 1715, 1690, 1543, 1266 cm^{-1}. ^{1}H NMR δ: 2.68 (t, *J* = 12.8 Hz, 1H), 3.07

(dd, *J* = 12.8, 6.0 Hz, 1H), 3.47 (s, 3H), 3.58 (s, 3H), 3.59-3.67 (m, 1H), 4.09 (dd, *J* =

9.8, 7.2 Hz, 1H), 4.32 (d, *J* = 11.5 Hz, 1H), 5.00 (d, *J* = 8.5 Hz, 1H), 5.98 (dd, *J* = 11.5,

8.5 Hz, 1H), 6.28 (dd, *J* = 15.5, 9.8 Hz, 1H), 6.38 (d, *J* = 15.5 Hz, 1H), 7.21-7.45 (m,

15H). ^{13}C NMR δ: 35.7, 51.2, 52.2, 60.0, 65.0, 66.5, 79.1, 96.0, 125.0, 126.9, 127.2,

128.5, 128.9, 129.0, 132.7, 136.1, 137.3, 139.3, 171.1, 172.9. MS (EI) *m/z*: 526 (M$^+$,

<1%), 480 (25), 467 (38), 232 (89), 193 (100), 169 (18), 141 (28), 128 (15), 115 (50),

91 (22). HRMS calculated for C$_{31}$H$_{30}$N$_2$O$_6$: 526.2104; found: 526.2104.

Trimethyl   (1S,2S,3S,5S,6R,7R,7aR)-6-nitro-5,7-diphenyl-3-[(E)-

styryl]tetrahydro-1H-pyrrolizine-1,2,7a(5H)-tricarboxylate   (endo-2e):   The

representative procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg), cinnamaldehyde (0.1 mmol, 12.6 µL) and the dimethyl fumarate (0.1 mmol, 14.4 mg). The desired product was obtained as sticky colorless oil (27.9 mg, 48% yield), $[\alpha]_D^{26}$ = +80.9 (*c* 0.8, CHCl$_3$), IR (neat) v_{max}: 1717, 1700, 1549, 1251 cm^{-1}. ^{1}H NMR δ: 3.37 (s, 3H), 3.59 (s, 3H), 3.61 (s, 3H), 3.89-3.98 (m, 2H), 4.17 (ddd, *J* = 9.8, 5.5, 2.1 Hz, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.99 (d, *J* = 8.3 Hz, 1H), 5.80 (dd, *J* = 11.4, 8.3 Hz, 1H), 6.22 (dd, *J* = 15.4, 9.8 Hz, 1H), 6.31 (d, *J* = 15.4 Hz, 1H), 7.27-7.41 (m, 15H). ^{13}C NMR δ: 51.7, 52.4, 52.5, 52.9, 53.7, 61.5, 63.0, 66.0, 79.6, 97.6, 124.6, 127.0, 128.2, 128.6, 128.7, 128.9, 129.0, 129.5, 132.1, 137.4, 139.0, 169.6, 170.5, 171.0. MS (EI) *m/z*: 584 (M$^+$, <1%), 538 (12), 440 (5), 394 (7), 290 (15), 193 (100), 193 (100), 115 (25). HRMS calculated for C$_{33}$H$_{32}$N$_2$O$_8$: 584.2159; found: 584.2155.

Trimethyl (1R,2R,3S,5S,6R,7R,7aR)-6-nitro-5,7-diphenyl-3-[(E)-styryl]tetrahydro-1H-pyrrolizine-1,2,7a(5H)-tricarboxylate (exo-2e): This minor product was obtained as sticky colorless oil (15.1 mg, 26% yield), $[\alpha]_D^{26}$ = +31.8 (*c* 0.5, CHCl$_3$), IR (neat) v_{max}: 1712, 1699, 1547, 1250 cm^{-1}. ^{1}H NMR δ: 3.60 (s, 3H), 3.68 (s, 6H), 3.84 (dd, *J* = 11.0, 10.9 Hz, 1H), 4.07-4.13 (m, 1H), 4.14 (d, *J* = 11.0 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 4.82 (d, *J* = 8.9 Hz, 1H), 5.42 (dd, *J* = 11.6, 8.9 Hz, 1H), 5.84 (dd, *J* = 15.9, 7.4 Hz, 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.90-6.94 (m, 2H), 7.15-7.30 (m, 11H), 7.43-7.48 (m, 2H). ^{13}C NMR δ: 51.2, 52.5, 52.6, 52.8, 53.4, 54.5, 66.2, 67.7, 79.5, 95.6, 123.5, 126.6, 127.3, 128.2, 128.5, 128.6, 128.7, 128.9, 132.4, 133.5, 134.8, 136.0, 139.6, 171.4, 171.6, 172.4. MS (EI) *m/z*: 584 (M$^+$, 4%), 538 (28), 525 (49), 314 (18), 290 (72), 258 (19), 230 (25), 194 (19), 193 (100), 115 (62), 91 (22). HRMS calculated for C$_{33}$H$_{32}$N$_2$O$_8$: 584.2159; found: 584.2154.

Trimethyl (1R,2R,3S,5S,7aR)-2-nitro-1,3-diphenyl-5-[(E)-styryl]-2,3-dihydro-1H-pyrrolizine-6,7,7a(5H)-tricarboxylate (2f): The representative procedure was

followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg), cinnamaldehyde (0.1 mmol, 12.6 µL) and dimethyl acetylenedicarboxylate (0.1 mmol, 9.1 µL). The desired product was obtained as sticky yellow oil (17.8 mg, 31% yield), $[\alpha]_D^{27}$ = +131.2 (*c* 1.0, CHCl$_3$), IR (neat) v_{max}: 1734, 1555, 1435, 1265, 1227 cm^{-1}. ^{1}H NMR δ: 3.51 (s, 3H), 3.60 (s, 3H), 3.76 (s, 3H), 4.59 (d, *J* = 11.5 Hz, 1H), 5.01 (d, *J* = 8.4 Hz, 1H), 5.08 (d, *J* = 9.3 Hz, 1H), 5.55 (dd, *J* = 11.5, 8.4 Hz, 1H), 6.05 (dd, *J* = 15.7, 9.3 Hz, 1H), 6.44 (d, *J* = 15.7 Hz, 1H), 7.14-7.45 (m, 15H). ^{13}C NMR δ: 52.2, 52.6, 52.7, 59.1, 66.4, 69.6, 85.4, 97.3, 126.3, 122.4, 126.9, 127.0, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.5, 132.9, 135.6, 137.2, 137.9, 139.4, 143.1, 163.2, 163.9, 170.6. MS (EI) *m/z*: 582 (M$^+$, <1%), 523 (14), 194 (17), 193 (100), 115 (23). HRMS calculated for C$_{33}$H$_{30}$N$_2$O$_8$: 582.2002; found: 582.2010.

6,7-Diethyl 7a-methyl (1R,2R,3S,5S,7aR)-2-nitro-1,3-diphenyl-5-[(E)-styryl]-2,3-dihydro-1H-pyrrolizine-6,7,7a(5H)-tricarboxylate ***(2g)***: The representative procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg), cinnamaldehyde (0.1 mmol, 12.6 µL) and diethyl acetylenedicarboxylate (0.1 mmol, 16.0 µL). The desired product was obtained as colorless needles (21.9 mg, 35% yield), mp 87-90 ºC (Et$_2$O), $[\alpha]_D^{28}$ = +141.9 (*c* 0.7, CHCl$_3$), IR (neat) v_{max}: 1744, 1722, 1555, 1286, 1270, 1227 cm^{-1}. ^{1}H NMR δ: 1.04 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 3.49 (s, 3H), 3.98-4.25 (m, 4H), 4.61 (d, *J* = 11.5 Hz, 1H), 5.02 (d, *J* = 8.4 Hz, 1H), 5.08 (d, *J* = 9.4 Hz, 1H), 5.56 (dd, *J* = 11.5, 8.4 Hz, 1H), 6.07 (dd, *J* = 15.7, 9.4 Hz, 1H), 6.45 (d, *J* = 15.7 Hz, 1H), 7.14-7.19 (m, 2H), 7.25-7.45 (m, 13H). ^{13}C NMR δ: 13.8, 14.2, 52.4, 59.2, 61.4, 61.8, 66.4, 69.7, 85.4, 97.3, 122.7, 126.9, 127.0, 128.4, 128.6, 128.7, 128.8, 129.6, 133.0, 135.6, 137.0, 137.7, 139.5, 143.0, 162.8, 163.5, 170.6. MS (EI) *m/z*: 610 (M$^+$, <1%), 551 (11), 194 (17), 193 (100), 115 (22). HRMS calculated for C$_{35}$H$_{34}$N$_2$O$_8$: 610.2315; found: 610.2323.

Methyl (3aS,4S,6S,7R,8R,8aR,8bR)-4-(2,2-diphenylvinyl)-7-nitro-1,3-dioxo-2,6,8-triphenyloctahydropyrrolo[3,4-a]pyrrolizine-8a(6H)-carboxylate (endo-2h): The representative procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg), β-phenylcinnamaldehyde (0.1 mmol, 20.8 mg) and *N*-phenylmaleimide (0.1 mmol, 17.3 mg). The desired product was obtained as colorless prisms (40.5 mg, 59% yield), mp 239-242 ºC (Et$_2$O), $[\alpha]_D^{27}$ = +25.1 (*c* 1.0, CHCl$_3$), IR (neat) v_{max}: 1710, 1552, 1497, 1372, 1265, 1215 cm^{-1}. ^{1}H NMR δ: 3.31 (s, 3H), 3.55 (dd, *J* = 8.3, 8.2 Hz, 1H), 4.19 (dd, *J* = 10.9, 8.3 Hz, 1H), 4.46 (d, *J* = 8.2 Hz, 1H), 4.94 (d, *J* = 8.6 Hz, 1H), 5.09 (d, *J* = 10.7 Hz, 1H), 5.60 (dd, *J* = 10.7, 8.6 Hz, 1H), 5.93 (d, *J* = 10.9 Hz, 1H), 6.74-6.78 (m, 2H), 7.00-7.55 (m, 23H). ^{13}C NMR δ: 51.8, 52.0, 52.7, 52.9, 60.5, 68.2, 82.8, 95.9, 121.1, 126.6, 127.1, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.5, 128.6, 128.8, 129.0, 129.1, 129.3, 129.4, 129.7, 131.7, 133.8, 138.4, 138.5, 141.3, 146.6, 171.4, 174.7, 175.9. MS (EI) *m/z*: 689 (M$^+$, 1%), 630 (28), 583 (24), 517 (27), 516 (74), 471 (16), 470 (43), 256 (18), 193 (61), 191 (100), 178 (19), 115 (41), 91 (20). HRMS calculated for C$_{43}$H$_{35}$N$_2$O$_4$ [M–NO$_2$]: 643.2597; found: 643.2628.

Methyl (3aR,4S,6S,7R,8R,8aR,8bS)-4-(2,2-diphenylvinyl)-7-nitro-1,3-dioxo-2,6,8-triphenyloctahydropyrrolo[3,4-a]pyrrolizine-8a(6H)-carboxylate (exo-2h): This minor product was obtained as yellow prisms (14.7 mg, 21% yield), mp 111-113 ºC (Et$_2$O), $[\alpha]_D^{26}$ = +66.9 (*c* 0.5, CHCl$_3$), IR (neat) v_{max}: 1711, 1552, 1495, 1375, 1259, 1182, 1028 cm^{-1}. ^{1}H NMR δ: 3.17 (s, 3H), 3.93 (dd, *J* = 10.2, 6.6 Hz, 1H), 4.25 (d, *J* = 10.2 Hz, 1H), 4.55 (dd, *J* = 10.5, 6.6 Hz, 1H), 4.60 (d, *J* = 9.4 Hz, 1H), 5.07 (d, *J* = 7.7 Hz, 1H), 5.47 (dd, *J* = 9.4, 7.9 Hz, 1H), 5.84 (d, *J* = 10.5 Hz, 1H), 6.69-6.80 (m, 2H), 6.92-6.99 (m, 2H), 7.13-7.56 (m, 21H). ^{13}C NMR δ: 52.3, 54.7, 56.4, 57.9, 61.3, 67.9, 83.2, 96.9, 124.0, 126.6, 126.7, 127.1, 127.5, 127.6, 127.7, 128.0, 128.1, 128.2, 128.3, 128.7, 128.8, 128.9, 129.0, 129.2, 129.3, 129.4, 129.6, 132.1, 134.7, 138.2, 139.3,

141.3, 147.5, 169.1, 173.2, 174.5. MS (EI) *m/z*: 689 (M$^+$, <1%), 643 (14), 517 (13), 516 (37), 471 (12), 470 (32), 256 (13), 194 (16), 193 (100), 192 (26), 191 (68), 178 (17), 167 (17), 115 (42), 91 (16). HRMS calculated for $C_{43}H_{35}N_2O_4$ [M–NO$_2$]: 643.2597; found: 643.2628.

Methyl (3aS,4S,6S,7R,8R,8aR,8bR)-8-(4-methoxyphenyl)-7-nitro-1,3-dioxo-2,6-diphenyl-4-((E)-styryl)octahydropyrrolo[3,4-a]pyrrolizine-8a(6H)-carboxylate (exo-2i): The representative procedure was followed by using *exo*-nitroprolinate **1b** (0.1 mmol, 35.6 mg), cinnamaldehyde (0.1 mmol, 12.6 µL) and *N*-phenylmaleimide (0.1 mmol, 17.3 mg). The desired product was obtained as yellow prisms (38.5 mg, 60% yield), mp 98-101 ºC (Et$_2$O), $[\alpha]_D^{27}$ = -48.3 (*c* 1.0, CHCl$_3$), IR (neat) ν_{max}: 1711, 1552, 1517, 1496, 1373, 1254, 1180, 735 cm^{-1}. ^{1}H NMR δ: 3.31 (s, 3H), 3.75 (s, 3H), 3.93 (dd, *J* = 10.1, 6.5 Hz, 1H), 4.19 (d, *J* = 10.1 Hz, 1H), 4.52-4.58 (m, 2H), 4.88 (d, *J* = 7.7 Hz, 1H), 5.45 (dd, *J* = 9.3, 7.7 Hz, 1H), 5.93 (dd, *J* = 15.7, 8.0 Hz, 1H), 6.53 (d, *J* = 15.7, Hz, 1H), 6.84-6.93 (m, 4H), 7.16-7.49 (m, 15H). ^{13}C NMR δ: 52.5, 53.3, 55.3, 55.8, 57.6, 65.8, 68.1, 83.3, 97.3, 114.3, 125.3, 126.2, 126.5, 126.7, 126.8, 128.2, 128.5, 128.6, 128.7, 128.8, 129.1, 129.2, 132.1, 134.3, 134.8, 135.9, 139.3, 159.3, 169.4, 173.4, 175.0. MS (EI) *m/z*: 644 (M$^+$, <1%), 224 (17), 223 (100). HRMS calculated for $C_{38}H_{34}N_3O_7$ [M+H]: 644.2397; found: 644.2394.

Methyl (3aR,4S,6S,7R,8R,8aR,8bS)-8-(4-methoxyphenyl)-7-nitro-1,3-dioxo-2,6-diphenyl-4-[(E)-styryl]octahydropyrrolo[3,4-a]pyrrolizine-8a(6H)-carboxylate (endo-2i): This minor product was obtained as yellow prisms (17.9 mg, 28% yield), mp 181-184 ºC (Et$_2$O), $[\alpha]_D^{26}$ = -100.4 (*c* 0.9, CHCl$_3$), IR (neat) ν_{max}: 1710, 1554, 1514, 1495, 1377, 1252, 1178, 1032, 756 cm^{-1}. ^{1}H NMR δ: 3.43 (s, 3H), 3.71 (dd, *J* = 8.3, 7.9 Hz, 1H), 3.78 (s, 3H), 4.25 (dd, *J* = 10.2, 7.9 Hz, 1H), 4.57 (d, *J* = 8.3 Hz, 1H), 4.84 (d, *J* = 8.5 Hz, 1H), 4.92 (d, *J* = 10.7 Hz, 1H), 5.49 (dd, *J* = 10.7, 8.5 Hz, 1H), 6.01 (dd, *J* =

15.4, 10.3 Hz, 1H), 6.35 (d, J = 15.4, Hz, 1H), 6.81-6.91 (m, 4H), 7.09-7.24 (m, 3H), 7.38-7.59 (m, 12H). ^{13}C NMR δ: 51.9, 53.1, 53.2, 55.4, 65.1, 68.2, 82.9, 96.5, 114.2, 114.4, 122.5, 125.5, 126.6, 126.7, 127.0, 128.2, 128.3, 129.0, 129.3, 129.6, 129.7, 131.7, 135.9, 138.5, 159.6, 171.6, 174.5, 175.9. MS (EI) m/z: 644 (M$^+$, <1%), 224 (17), 223 (100), 115 (13). HRMS calculated for $C_{38}H_{33}N_2O_5$ [M–NO$_2$]: 597.2389; found: 597.2363.

Methyl (3aS*,4S*,6S*,7S*,8S*,8aR*,8bR*)-8-cyclohexil-7-nitro-1,3-dioxo-2,6-diphenyl-4-[(E)-styryl]octahydropyrrolo[3,4-a]pyrrolizine-8a(6H)-carboxylate (exo-2k): The representative procedure was followed by using *rac-endo*-nitroprolinate **1c** (0.1 mmol, 33.2 mg), cinnamaldehyde (0.1 mmol, 12.6 µL) and *N*-phenylmaleimide (0.1 mmol, 17.3 mg). The desired product was obtained as sticky yellow oil (45.0 mg, 72% yield), IR (neat) ν_{max}: 1712, 1550, 1371, 1184, 908, 729 cm^{-1}. ^{1}H NMR δ: 1.10-1.25 (m, 4H), 1.54-1.76 (m, 4H), 2.06-2.27 (m, 2H), 3.07 (t, J = 9.8 Hz, 1H), 3.54 (s, 3H), 3.83 (dd, J = 9.9, 5.1 Hz, 1H), 3.92 (d, J = 9.9 Hz, 1H), 4.53 (ddd, J = 8.8, 5.1, 1.0 Hz, 1H), 4.71 (d, J = 6.7 Hz, 1H), 5.11 (dd, J = 9.7, 6.7 Hz, 1H), 6.03 (dd, J = 15.6, 8.8 Hz, 1H), 6.55 (d, J = 15.6 Hz, 1H), 7.08-7.13 (m, 2H), 7.20-7.53 (m, 13H). ^{13}C NMR δ: 25.9, 26.0, 26.2, 30.5, 32.4, 39.3, 52.6, 53.9, 54.9, 61.6, 66.1, 68.3, 81.8, 99.0, 125.9, 126.5, 126.8, 128.2, 128.3, 128.6, 128.7, 128.9, 129.2, 132.2, 135.5, 135.7, 140.4, 170.1, 173.9, 174.8. MS (EI) m/z: 619 (M$^+$, 2%), 574 (40), 573 (100), 561 (18), 560 (48), 514 (16), 513 (40), 446 (14), 432 (17), 431 (53), 317 (24), 284 (18), 258 (20), 180 (43), 157 (20), 141 (27), 117 (44), 115 (44), 91 (35). HRMS calculated for $C_{37}H_{37}N_2O_4$ [M–NO$_2$]: 573.2753; found: 573.2753.

General procedure for the synthesis of AAD products 3a-3n: To a stirred solution of the nitroprolinate **1** (0.1 mmol) in toluene (1 mL) the aldehyde (0.1 mmol) and the dienophile (0.1 mmol) were added. The reaction mixture was stirred overnight

at room temperature and the solvent was evaporated under reduced pressure. The crude

mixture was purified by flash column chromatography over silica gel (20% EtOAc in

hexane as the eluent) to furnish the corresponding product.

Methyl (2S,3S,4R,5S)-1-[(3aS,4R,7aS)-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (3a): The

representative procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6

mg), crotonaldehyde (0.1 mmol, 8.3 µL) and *N*-methylmaleimide (0.2 mmol, 22.2 mg).

The desired product was obtained as colorless prisms (46.1 mg, 94% yield), mp 205-

209 °C (Et$_2$O), $[\alpha]_D^{26}$ = 95.5 (*c* 1.0, CHCl$_3$), IR (neat) ν_{max}: 1739, 1697, 1551, 1436,

1200, 1155 cm^{-1}. ^{1}H NMR δ: 1.81-1.99 (m, 1H), 2.70 (ddd, *J* = 15.7, 7.1, 1.7 Hz, 1H),

3.01 (td, *J* = 8.9, 7.1 Hz, 1H), 3.04 (s, 3H), 3.29 (s, 3H), 3.43 (dd, *J* = 8.9, 6.2 Hz, 1H),

3.62 (dd, *J* = 6.1, 3.1 Hz, 1H), 4.39 (d, *J* = 9.4 Hz, 1H), 5.06 (dd, *J* = 12.1, 9.4 Hz, 1H),

5.21 (d, *J* = 8.5 Hz, 1H), 5.61 (dd, *J* = 12.1, 8.5 Hz, 1H), 5.72 (dt, *J* = 9.7, 3.1 Hz, 1H),

5.87 (ddt, *J* = 9.8, 7.1, 3.0 Hz, 1H), 7.28-7.32 (m, 5H), 7.40-7.44 (m, 3H), 7.63-7.68 (m,

2H). ^{13}C NMR δ: 23.5, 25.3, 38.9, 39.4, 51.0, 51.8, 53.1, 66.0, 68.3, 92.5, 127.7, 128.0,

128.3, 128.6, 128.7, 129.4, 133.0, 137.8, 174.4, 178.0, 179.5. MS (EI) *m/z*: 489 (M$^+$,

2%), 430 (13), 383 (22), 279 (22), 278 (100), 272 (24), 220 (57), 219 (36), 193 (19),

115 (29), 91 (14), 79 (28). HRMS calculated for C$_{27}$H$_{27}$N$_2$O$_4$ [M–NO$_2$]: 443.1971;

found: 443.1965.

Methyl (2S,3S,4R,5S)-1-[(3aS,4R,7aS)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (3b): The

representative procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6

mg), crotonaldehyde (0.1 mmol, 8.3 µL) and *N*-phenylmaleimide (0.1 mmol, 17.3 mg).

The desired product was obtained as colorless prisms (47.4 mg, 86% yield), mp 249-

251 °C (Et$_2$O), $[\alpha]_D^{26}$= +40.2 (*c* 1.0, CHCl$_3$), IR (neat) ν_{max}: 1700, 1555, 1387 cm^{-1}. ^{1}H

NMR δ: 1.89-2.06 (m, 1H), 2.79 (ddd, J = 15.7, 7.1, 1.7 Hz, 1H), 3.17 (ddd, J = 9.0, 7.4, 1.7 Hz, 1H), 3.29 (s, 3H), 3.60 (dd, J = 9.0, 6.9 Hz, 1H), 3.71 (dd, J = 6.9, 3.0 Hz, 1H), 4.44 (d, J = 9.3 Hz, 1H), 4.97 (dd, J = 12.1, 9.3 Hz, 1H), 5.24 (d, J = 8.5 Hz, 1H), 5.61 (dd, J = 12.1, 8.5 Hz, 1H), 5.84 (dt, J = 9.7, 3.0 Hz, 1H), 5.98 (ddt, J = 9.7, 7.1, 3.0 Hz, 1H), 7.18-7.32 (m, 6H), 7.39-7.57 (m, 7H), 7.65-7.71 (m, 2H). ^{13}C NMR δ: 23.8, 39.0, 39.6, 50.9, 51.8, 53.3, 66.0, 68.3, 92.5, 126.7, 127.7, 128.0, 128.3, 128.7, 128.9, 129.0, 129.1, 129.4, 131.9, 132.8, 137.7, 174.3, 177.0, 178.5. MS (EI) m/z: 551 (M$^+$, <1%), 332 (13), 279 (22), 278 (100), 272 (23), 220 (37), 219 (25), 193 (12), 115 (21), 91 (12). HRMS calculated for $C_{32}H_{29}N_2O_4$ [M–NO$_2$]: 505.2127; found: 505.2121.

Methyl (2S,3S,4R,5S)-1-[(3aS,4R,7aS)-2-benzyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (3c): The representative procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg), crotonaldehyde (0.1 mmol, 8.3 μL) and *N*-benzylmaleimide (0.1 mmol, 18.7 mg). The desired product was obtained as colorless prisms (50.1 mg, 89% yield), mp 72-75 ºC (Et$_2$O), $[\alpha]_D^{27}$ = +63.7 (*c* 1.0, CHCl$_3$), IR (neat) ν_{max}: 1738, 1697, 1551, 1398, 1350, 1201, 1159 cm^{-1}. ^{1}H NMR δ: 1.87 (ddd, J = 15.6, 6.7, 3.0 Hz, 1H), 2.75 (ddd, J = 15.6, 7.2, 1.8 Hz, 1H), 2.97-3.09 (m, 1H), 3.23 (s, 3H), 3.41 (dd, J = 8.9, 6.9 Hz, 1H), 3.61 (dd, J = 6.9, 3.0 Hz, 1H), 3.99 (d, J = 9.4 Hz, 1H), 4.63 (d, J = 14.2 Hz, 1H), 4.81 (d, J = 14.2 Hz, 1H), 4.94 (dd, J = 12.1, 9.4 Hz, 1H), 5.22 (d, J = 8.5 Hz, 1H), 5.66-5.51 (m, 2H), 5.88 (ddt, J = 10.1, 6.7, 3.0 Hz, 1H), 7.07-7.15 (m, 2H), 7.20-7.47 (m, 11H), 7.58-7.68 (m, 2H). ^{13}C NMR δ: 23.3, 39.2, 39.8, 42.8, 50.7, 51.7, 53.2, 65.8, 68.2, 92.3, 127.7, 127.9, 128.0, 128.2, 128.4, 128.6, 128.9, 129.0, 129.4, 132.9, 135.7, 137.9, 174.3, 177.4, 179.0. MS (EI) m/z: 565 (M$^+$, <1%), 332 (9), 279 (21), 278 (100), 272 (17), 220 (33), 219 (23), 115 (15), 91 (26), 79 (18). HRMS calculated for $C_{33}H_{31}N_2O_4$ [M–NO$_2$]: 519.2284; found: 519.2266.

Methyl (2S,3S,4R,5S)-1-[(3aS,4R,7aS)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (3d): The representative procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg), crotonaldehyde (0.1 mmol, 8.3 μL) and maleimide (0.1 mmol, 9.7 mg). The desired product was obtained as colorless prisms (37.8 mg, 80% yield), mp 87-91 ℃ (Et$_2$O), $[\alpha]_D^{26}$= +90.5 (*c* 1.0, CHCl$_3$), IR (neat) ν_{max}: 1699, 1551, 1353, 1199, 1162 cm^{-1}. ^{1}H NMR δ: 1.89 (ddd, *J* = 15.6, 7.2, 2.9 Hz, 1H), 2.68 (ddd, *J* = 15.6, 7.0, 1.7 Hz, 1H), 3.09 (ddd, *J* = 9.0, 7.2, 1.7 Hz, 1H), 3.30 (s, 3H), 3.49 (dd, *J* = 9.0, 7.0 Hz, 1H), 3.63 (dd, *J* = 7.0, 3.0 Hz, 1H), 4.46 (d, *J* = 9.3 Hz, 1H), 5.01 (dd, *J* = 12.1, 9.3 Hz, 1H), 5.19 (d, *J* = 8.5 Hz, 1H), 5.62 (dd, *J* = 12.1, 8.5 Hz, 1H), 5.79 (dt, *J* = 9.8, 3.0 Hz, 1H), 5.94 (ddt, *J* = 9.8, 7.0, 2.9 Hz, 1H), 7.19-7.36 (m, 5H), 7.35-7.49 (m, 3H), 7.62-7.70 (m, 2H), 9.06 (br s, 1H). ^{13}C NMR δ: 23.3, 40.3, 40.6, 51.0, 51.9, 53.1, 66.0, 68.3, 92.5, 127.7, 127.8, 128.1, 128.4, 128.6, 128.8, 129.4, 132.8, 137.8, 174.4, 178.5, 180.1. MS (EI) *m/z*: 475 (M$^+$, <1%), 429 (11), 428 (16), 416 (17), 378 (19), 369 (44), 332 (28), 279 (24), 278 (100), 272 (50), 221 (16), 220 (96), 219 (79), 193 (21), 115 (43), 91 (20), 79 (42), 77 (19). HRMS calculated for C$_{26}$H$_{25}$N$_2$O$_4$ [M–NO$_2$]: 429.1814; found: 429.1804.

Methyl (2S,3S,4R,5S)-1-[(3aS,4R,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydroisobenzofuran-4-yl]-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (3e, isolated as 63:27 mixture of diastereoisomers): The representative procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg), crotonaldehyde (0.1 mmol, 8.3 μL) and maleic anhydride (0.1 mmol, 9.8 mg). The desired product was obtained as sticky yellow oil (33.9 mg, 71% yield). Data for the major isomer: IR (neat) ν_{max}: 1774, 1739, 1552, 1203, 910, 731 cm^{-1}. ^{1}H NMR δ: 1.93-2.04 (m, 1H), 2.71 (ddd, *J* = 16.1, 7.0, 2.0 Hz, 1H), 3.28 (s, 3H), 3.34-3.38 (m, 1H), 3.63-3.70 (m, 2H), 4.40 (d, *J* = 9.2 Hz, 1H), 4.89 (dd, *J* = 12.1, 9.2 Hz, 1H), 5.11 (d, *J* = 8.5 Hz, 1H), 5.62 (dd, *J* =

12.1, 8.5 Hz, 1H), 5.77-5.86 (m, 1H), 6.01 (ddt, *J* = 12.4, 6.8, 2.7 Hz, 1H), 7.04-7.51

(m, 13H), 7.58-7.77 (m, 2H). ^{13}C NMR δ: 23.4, 39.9, 40.3, 51.1, 52.0, 52.6, 65.6, 68.3,

92.2, 127.2, 127.7, 127.8, 128.0, 128.5, 128.7, 128.8, 129.3, 129.5, 129.6, 130.1, 132.4,

137.4, 172.1, 173.7, 174.1. MS (EI) *m/z*: 476 (M$^+$, <1%), 378 (10), 280 (16), 279 (18),

221 (19), 220 (100), 219 (19), 193 (56), 117 (20), 115 (43), 91 (16). HRMS calculated

for $C_{24}H_{20}NO_3$ [M–NO$_2$, –HCO$_2$Me]: 370.1443; found: 370.1451.

(2S,3S,4R,5S)-1-((1R,5R,6R)-5,6-bis(phenylsulfonyl)cyclohex-2-en-1-yl)-2-

((methylperoxy)-λ^2-methyl)-4-nitro-3,5-diphenylpyrrolidine (3g): The representative

procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg),

crotonaldehyde (0.1 mmol, 8.3 μL) and *trans*-1,2-bis(phenylsulfonyl)ethylene (0.1

mmol, 30.8 mg). The desired product was obtained as yellow prisms as a 1:0.5

endo/exo-mixture (53.5 mg, 78% yield), mp 94-97 ºC (Et$_2$O), IR (neat) ν_{max}: 1737,

1551, 1447, 1308, 1204, 1146, 1081, 756 cm^{-1}. ^{1}H NMR δ [mixture of *endo/exo*

(1:0.5)]: 2.27-2.42 (m, 1H), 2.43-2.52 (m, 1.5H), 2.71-2.78 (m, 0.5H), 3.01-3.05 (m,

0.5H), 3.24 (s, 1.5H), 3.25 (s, 3H), 3.72-3.77 (m, 0.5H), 3.80-3.85 (m, 1.5H), 4.15 (br s,

1H), 4.24-4.27 (m, 0.5H), 4.61 (dd, *J* = 12.0, 9.2 Hz, 1H), 4.68-4.73 (m, 0.5H), 4.81 (d,

J = 8.6 Hz, 0.5H), 4.89 (d, *J* = 9.3 Hz, 1H), 5.03 (d, *J* = 8.3 Hz, 1H), 5.10 (d, *J* = 8.4 Hz,

0.5H), 5.59 (dd, *J* = 12.0, 8.4 Hz, 2H), 5.71-5.83 (m, 1.5H), 5.99 (ddq, *J* = 10.7, 5.4, 2.7

Hz, 1H), 6.20 (d, *J* = 2.7 Hz, 0.5H), 6.93-6.97 (m, 0.5H), 7.20-7.86 (m, 35H). ^{13}C NMR

δ [mixture of *endo*/*exo* (1:0.5), data of the major *endo*-diastereoisomer]: 20.7, 48.3,

51.7, 52.5, 55.9, 58.7, 64.7, 68.6, 92.6, 126.1, 126.6, 127.4, 127.8, 128.1, 128.4, 128.7,

128.8, 129.0, 129.5, 129.8, 129.9, 130.1, 132.8, 134.5, 134.6, 136.3, 138.6, 138.7,

174.0. MS (EI) *m/z*: 687 (M$^+$, <1%), 404 (24), 403 (89), 296 (27), 221 (20), 220 (100),

219 (41), 193 (31), 164 (21), 141 (43), 125 (57), 115 (46), 104 (19), 91 (20), 79 (33), 78

(24), 77 (87). HRMS calculated for $C_{36}H_{35}N_2O_8S_2$ [M+H]: 687.1835; found: 687.1837.

Methyl (2S,3S,4R,5S)-1-[(3aS,4R,7aS)-6-methyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (3i): The representative procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg), 3-methylcrotonaldehyde (0.1 mmol, 9.7 µL) and *N*-phenylmaleimide (0.1 mmol, 17.3 mg). The desired product was obtained as colorless prisms (35.2 mg, 62% yield), mp 228-232 °C (Et$_2$O), $[\alpha]_D^{29}$= +73.1 (*c* 1.0, CHCl$_3$), IR (neat) ν_{max}: 1746, 1705, 1548, 1500, 1384 cm^{-1}. ^{1}H NMR δ: 1.75 (s, 3H), 2.02 (dd, *J* = 15.2, 7.3 Hz, 1H), 2.62 (dd, *J* = 15.3, 2.1 Hz, 1H), 3.17 (ddd, *J* = 9.0, 7.0, 2.0 Hz, 1H), 3.30 (s, 3H), 3.54 (dd, *J* = 9.0, 6.9 Hz, 1H), 3.68 (br s, 1H), 4.40 (d, *J* = 9.3 Hz, 1H), 4.95 (dd, *J* = 12.0, 9.3 Hz, 1H), 5.24 (d, *J* = 8.5 Hz, 1H), 5.44 (br s, 1H), 5.60 (dd, *J* = 12.0, 8.5 Hz, 1H), 7.12-7.35 (m, 7H), 7.37-7.58 (m, 6H), 7.64-7.71 (m, 2H). ^{13}C NMR δ: 23.6, 28.8, 39.3, 39.7, 50.9, 51.8, 54.0, 66.0, 68.5, 92.5, 121.0, 126.6, 127.8, 128.1, 128.3, 128.7, 129.0, 129.4, 132.0, 133.0, 138.0, 138.3, 174.5, 177.1, 178.4. MS (EI) *m/z*: 566 (M$^+$, <1%), 346 (33), 286 (14), 279 (25), 278 (100), 220 (45), 115 (16), 93 (35), 91 (18). HRMS calculated for C$_{33}$H$_{31}$N$_3$O$_6$: 565.2213; found: 565.2199.

Methyl (2S,3S,4R,5S)-1-[(3aS,4R,7S,7aS)-7-methyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (3j): The representative procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg), *trans*-2-pentenal (0.1 mmol, 10.3 µL) and *N*-phenylmaleimide (0.1 mmol, 17.3 mg). The desired product was obtained as colorless plates (50.6 mg, 89% yield), mp 244-247 °C (Et$_2$O), $[\alpha]_D^{26}$ = +104.3 (*c* 1.0, CHCl$_3$), IR (neat) ν_{max}: 1699, 1552, 1385, 1192, 1032, 762 cm^{-1}. ^{1}H NMR δ: 1.44 (d, *J* = 7.3 Hz, 3H), 2.20-2.30 (m, 1H), 3.06 (dd, *J* = 8.7, 6.5 Hz, 1H), 3.31 (s, 3H), 3.58 (dd, *J* = 8.7, 6.9 Hz, 1H), 3.67-3.73 (m, 1H), 4.48 (d, *J* = 9.3 Hz, 1H), 4.97 (dd, *J* = 12.1, 9.3 Hz, 1H), 5.24 (d, *J* = 8.5 Hz, 1H), 5.61 (dd, *J* = 12.1, 8.5 Hz, 1H), 5.73-5.87 (m, 2H), 7.19-7.28 (m, 7H), 7.41-

7.56 (m, 6H), 7.62-7.71 (m, 2H). ^{13}C NMR δ: 16.7, 30.6, 40.4, 44.0, 50.9, 51.9, 53.9, 66.2, 68.3, 92.6, 126.8, 127.4, 127.7, 128.1, 128.3, 128.7, 129.0, 129.4, 129.5, 131.9, 132.9, 135.5, 137.7, 174.3, 176.3, 176.7. MS (EI) *m/z*: 566 (M$^+$, <1%), 393 (12), 392 (45), 346 (21), 286 (44), 279 (21), 278 (100), 220 (36), 219 (17), 115 (23), 93 (34), 91 (24). HRMS calculated for $C_{33}H_{31}N_2O_4$ [M–NO$_2$]: 519.2284; found: 519.2275.

Methyl (2S,3S,4R,5S)-1-[(3aS,4R,7S,7aS)-7-ethyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (3k): The representative procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg), *trans*-2-hexenal (0.1 mmol, 11.8 μL) and *N*-phenylmaleimide (0.1 mmol, 17.3 mg). The desired product was obtained as yellow prisms (41.7 mg, 72% yield), mp 201-204 ºC (Et$_2$O), $[\alpha]_D^{26}$ = +84.3 (*c* 1.0, CHCl$_3$), IR (neat) ν_{max}: 1699, 1552, 1385, 1188, 1030, 758 cm^{-1}. ^{1}H NMR δ: 0.99 (t, *J* = 7.0 Hz, 3H), 1.79-2.02 (m, 3H), 3.17 (dd, *J* = 8.7, 5.4 Hz, 1H), 3.31 (s, 3H), 3.57 (dd, *J* = 8.7, 7.1 Hz, 1H), 3.71 (d, *J* = 7.1 Hz, 1H), 4.46 (d, *J* = 9.4 Hz, 1H), 4.98 (dd, *J* = 12.1, 9.4 Hz, 1H), 5.27 (d, *J* = 8.5 Hz, 1H), 5.61 (dd, *J* = 12.1, 8.5 Hz, 1H), 5.81-5.90 (m, 2H), 7.16-7.31 (m, 6H), 7.38-7.58 (m, 7H), 7.63-7.73 (m, 2H). ^{13}C NMR δ: 12.7, 24.1, 37.9, 40.3, 42.4, 50.9, 51.9, 54.1, 66.3, 68.3, 92.6, 126.8, 127.6, 127.8, 128.0, 128.1, 128.3, 128.7, 129.0, 129.4, 129.5, 131.9, 132.9, 134.5, 137.8, 174.3, 176.2, 176.7. MS (EI) *m/z*: 580 (M$^+$, <1%), 407 (15), 406 (53), 360 (21), 300 (37), 279 (21), 278 (100), 220 (39), 193 (16), 115 (26), 107 (18), 91 (19), 79 (27). HRMS calculated for $C_{34}H_{33}N_2O_4$ [M–NO$_2$]: 533.2440; found: 533.2429.

Methyl (2S,3S,4R,5S)-1-[(3aS,4R,7aS)-6-(4-methylpent-3-en-1-yl)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (3l): The representative procedure was followed by using *exo*-nitroprolinate **1a** (0.1 mmol, 32.6 mg), geranial (0.1 mmol, 18.0 μL) and *N*-phenylmaleimide (0.1

mmol, 17.3 mg). The desired product was obtained as yellow plates (33.8 mg, 53%

yield), mp 117-120 ºC (Et$_2$O), $[\alpha]_D^{24}$ = +34.3 (*c* 0.6, CHCl$_3$), IR (neat) ν_{max}: 1743, 1703,

1549, 1375, 1163, 750 cm^{-1}. ^{1}H NMR δ: 1.54 (s, 3H), 1.64 (s, 3H), 1.93-2.10 (m, 5H),

2.67 (dd, *J* = 15.0, 1.9 Hz, 1H), 3.18 (ddd, *J* = 9.0, 7.2, 1.9 Hz, 1H), 3.30 (s, 3H), 3.56

(dd, *J* = 9.0, 6.8 Hz, 1H), 3.69 (br s, 1H), 4.44 (d, *J* = 9.4 Hz, 1H), 4.97 (dd, *J* = 12.0,

9.4 Hz, 1H), 4.97-5.03 (br s, 1H), 5.25 (d, *J* = 8.5 Hz, 1H), 5.45 (br s, 1H), 5.61 (dd, *J* =

12.0, 8.5 Hz, 1H), 7.20-7.33 (m, 7H), 7.41-7.56 (m, 6H), 7.66-7.71 (m, 2H). ^{13}C NMR

δ: 17.8, 25.8, 25.9, 27.9, 37.2, 39.2, 39.6, 50.9, 51.9, 54.0, 66.0, 68.4, 92.5, 120.6,

123.2, 126.6, 127.8, 128.1, 128.7, 129.0, 129.4, 129.5, 132.0, 132.5, 133.0, 137.9,

142.0, 174.5, 177.2, 178.4. MS (EI) *m/z*: 634 (M$^+$, <1%), 279 (27), 278 (100), 240 (13),

220 (37), 115 (15), 91 (18), 69 (17). HRMS calculated for C$_{38}$H$_{39}$N$_2$O$_4$ [M–NO$_2$]:

587.2910; found: 587.2895.

Methyl (2R,3S,4R,5S)-1-[(3aS,4R,7aS)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-

hexahydro-1H-isoindol-4-yl]-3-(4-methoxyphenyl)-4-nitro-5-diphenylpyrrolidine-2-

carboxylate (3m): The representative procedure was followed by using *exo-*

nitroprolinate **1b** (0.1 mmol, 35.6 mg), crotonaldehyde (0.1 mmol, 8.3 µL) and *N-*

phenylmaleimide (0.1 mmol, 17.3 mg). The desired product was obtained as orange

prisms (47.2 mg, 81% yield), mp 208-211 ºC (Et$_2$O), $[\alpha]_D^{25}$ = +86.3 (*c* 1.0, CHCl$_3$), IR

(neat) ν_{max}: 1745, 1702, 1550, 1517, 1388, 1254, 1156, 1024, 796, 761 cm^{-1}. ^{1}H NMR δ:

1.93-2.04 (m, 1H), 2.80 (ddd, *J* = 15.7, 7.0, 1.7 Hz, 1H), 3.18 (ddd, *J* = 9.0, 7.5, 1.7 Hz,

1H), 3.36 (s, 3H), 3.60 (dd, *J* = 9.0, 7.0 Hz, 1H), 3.71 (dd, *J* = 6.6, 3.0 Hz, 1H), 3.75 (s,

3H), 4.40 (d, *J* = 9.3 Hz, 1H), 4.90 (dd, *J* = 12.1, 9.3 Hz, 1H), 5.23 (d, *J* = 8.5 Hz, 1H),

5.54 (dd, *J* = 12.1, 8.5 Hz, 1H), 5.84 (dt, *J* = 9.7, 3.0 Hz, 1H), 5.98 (ddt, *J* = 10.0, 6.6,

3.0 Hz, 1H), 6.76-7.31 (m, 6H), 7.39-7.56 (m, 6H), 7.65-7.69 (m, 2H). ^{13}C NMR δ:

23.9, 39.0, 39.6, 50.4, 52.0, 53.4, 55.3, 66.0, 68.2, 93.0, 114.1, 124.7, 126.7, 127.7,

128.8, 128.9, 129.0, 129.2, 129.4, 131.9, 137.8, 159.5, 174.5, 177.0, 178.6. MS (EI)

m/z: 582 (M$^+$, >1%), 362 (13), 309 (23), 308 (100), 302 (22), 250 (29), 249 (37), 223

(25), 115 (13), 79 (24). HRMS calculated for $C_{33}H_{31}N_2O_5$ [M–NO$_2$]: 535.2233; found:

535.2222.

Methyl (2S*,3R*,4S*,5S*)-3-cyclohexyl-1-[(3aS*,4R*,7aS*)-1,3-dioxo-2-

phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]-4-nitro-5-phenylpyrrolidine-2-

carboxylate (3n): The representative procedure was followed by using *rac-endo-*

nitroprolinate **1c** (0.1 mmol, 33.2 mg), crotonaldehyde (0.1 mmol, 8.3 μL) and *N-*

phenylmaleimide (0.1 mmol, 17.3 mg). The desired product was obtained as colorless

prisms (26.5 mg, 79% yield), mp 76-80 ºC (Et$_2$O), IR (neat) ν_{max}: 1705, 1551, 1380,

1166 cm^{-1}. ^{1}H NMR δ [mixture of diastereoisomers (1:1)]: 0.75-0.94 (m, 4H), 0.98-1.18

(m, 8H), 1.51-1.81 (m, 12H), 1.96-2.14 (m, 1H), 2.69-2.93 (m, 1H), 3.07-3.22 (m, 1H),

3.30 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.44 (ddd, *J* = 11.3, 9.7, 5.8 Hz, 1H), 3.60 (dd, *J* = 9.1,

8.0 Hz, 1H), 3.80-4.00 (m with 2s at 3.82 and 3.90, 9H), 4.29 (d, *J* = 9.6 Hz, 1H), 4.75

(d, *J* = 9.4 Hz, 1H), 5.21 (d, *J* = 9.1 Hz, 1H), 5.34 (dd, *J* = 9.1, 8.3 Hz, 1H), 5.58-5.66

(m, 2H), 5.71-5.80 (m, 1H), 5.85 (dt, *J* = 10.0, 2.8 Hz, 1H), 5.90-5.99 (m, 1H), 7.21-

7.65 (m, 20H). ^{13}C NMR δ [mixture of diastereoisomers (1:1)]: 22.8, 23.4, 26.1, 26.4,

29.8, 30.1, 30.4, 30.7, 38.6, 38.8, 39.2, 39.4, 40.6, 48.4, 51.5, 52.5, 52.7, 54.7, 55.1,

64.0, 66.1, 68.0, 89.3, 90.5, 126.5, 127.6, 128.3, 128.5, 128.7, 128.9, 129.1, 129.2,

129.5, 137.2, 140.6, 173.6, 175.9, 176.7, 177.1, 178.4. MS (EI) *m/z*: 557 (M$^+$, <1%), 512

(35), 511 (100), 498 (22), 451 (22), 384 (38), 337 (37), 331 (40), 286 (57), 284 (26),

278 (46), 226 (45), 225 (32), 202 (67), 196 (48), 144 (64), 143 (24), 117 (27), 115 (18),

91 (24), 79 (87). HRMS calculated for $C_{32}H_{35}N_2O_4$ [M–NO$_2$]: 511.2597; found

511.2602.

*General procedure for the synthesis of pyrrolizidines endo-**15-18***: To a stirred solution of methyl prolinate **11-14** (0.1 mmol) in toluene (1 mL) crotonaldehyde (0.1 mmol, 8.3 µL) and *N*-phenylmaleimide (0.1 mmol, 17.3 mg) were added. The reaction mixture was stirred overnight at room temperature and the solvent was evaporated under reduced pressure. The crude mixture was purified by flash column chromatography over silica gel (20% EtOAc in hexane as the eluent) to furnish the corresponding product.

Methyl (3aS,4S*,8aR*,8bR*)-1,3-dioxo-2-phenyl-4-[(E)-prop-1-en-1-yl]octahydropyrrolo[3,4-a]-pyrrolizine-8a(6H)-carboxylate (endo-**15**):* The representative procedure was followed by using L-proline methyl ester **11** (0.1 mmol, 12.9 mg). The desired product was obtained as sticky yellow oil (21.6 mg, 61% yield), IR (neat) ν_{max}: 1707, 1498, 1376, 1215, 1176, 967, 733 cm^{-1}. ^{1}H NMR δ: 1.78 (dd, J = 6.5, 1.6 Hz, 3H), 1.80-1.98 (m, 1H), 1.99-2.15 (m, 1H), 2.36-2.44 (m, 1H), 2.59-2.72 (m, 2H), 3.18 (ddd, J = 10.4, 8.1, 3.0 Hz, 1H), 3.52 (t, J = 8.4 Hz, 1H), 3.81 (s, 3H), 4.04 (d, J = 8.4 Hz, 1H), 4.13 (t, J = 8.9 Hz, 1H), 5.71 (ddd, J = 15.0, 9.5, 1.6 Hz, 1H), 5.86-6.02 (m, 1H), 7.18-7.34 (m, 2H), 7.35-7.54 (m, 3H). ^{13}C NMR δ: 18.1, 24.8, 30.3, 48.9, 51.2, 51.6, 53.3, 65.5, 79.4, 124.2, 126.1, 126.6, 128.8, 129.2, 129.3, 131.8, 133.4, 173.9, 175.5, 176.0. MS (EI) *m/z*: 354 (M$^+$, <1%), 296 (19), 295 (100), 148 (14). HRMS calculated for $C_{20}H_{22}N_2O_4$: 354.1580; found: 354.1578.

*Methyl (3aS,4S,7R,8aR,8bR)-7-hydroxy-1,3-dioxo-2-phenyl-4-[(E)-prop-1-en-1-yl]octahydropyrrolo[3,4-a]-pyrrolizine-8a(6H)-carboxylate (endo-**16**):* The representative procedure was followed by using L-4-hydroxyproline methyl ester **12** (0.1 mmol, 14.5 mg). The desired product was obtained as sticky yellow oil (25.6 mg, 69% yield), $[\alpha]_D^{26}$ = -42.4 (*c* 0.6, CHCl$_3$), IR (neat) ν_{max}: 1705, 1377, 1178, 731 cm^{-1}. ^{1}H NMR δ: 1.79 (dd, J = 6.5, 1.6 Hz, 3H), 2.43 (d, J = 15.4 Hz, 1H), 2.82 (dd, J = 10.4, 4.2 Hz, 1H), 2.96 (dd, J = 15.4, 6.2 Hz, 1H), 3.03-3.32 (br s, 1H), 3.14 (d, J = 10.4 Hz, 1H),

3.61 (t, J = 8.4 Hz, 1H), 3.86 (s, 3H), 4.09 (d, J = 8.4 Hz, 1H), 4.18 (t, J = 9.0 Hz, 1H), 4.40 (t, J = 5.2 Hz, 1H), 5.59 (ddd, J = 15.0, 9.6, 1.7 Hz, 1H), 5.88-6.02 (m, 1H), 7.17-7.23 (m, 2H), 7.37-7.54 (m, 3H). ^{13}C NMR δ: 18.2, 40.5, 50.7, 52.1, 53.8, 57.4, 64.7, 72.4, 77.9, 123.5, 126.1, 129.0, 129.4, 131.6, 134.2, 173.5, 175.0, 175.6. MS (EI) m/z: 370 (M$^+$, 1%), 312 (21), 311 (100). HRMS calculated for $C_{20}H_{22}N_2O_5$: 370.1529; found: 370.1516.

Methyl (3aR,3bR,3cR,6aS,7S,9R,9aS)-2-methyl-1,3,4,6-tetraoxo-5,9-diphenyl-7-[(E)-prop-1-en-1-yl]dodecahydro-3bH-dipyrrolo[3,4-a:3',4'-f]pyrrolizine-3b-carboxylate (endo-17): The representative procedure was followed by using proline ester derivative *endo*-**13** (0.1 mmol, 28.8 mg). The desired product was obtained as colorless prisms (34.3 mg, 67% yield), mp 223-227 ºC (Et$_2$O), $[\alpha]_D^{25}$ = +96.1 (*c* 0.9, CHCl$_3$), IR (neat) ν_{max}: 1705, 1436, 1379, 1177, 1060, 963, 733 cm^{-1}. ^{1}H NMR δ: 1.22 (dd, J = 6.5, 1.7 Hz, 3H), 2.77 (s, 3H), 3.41-3.46 (m, 1H), 3.48 (dd, J = 10.4, 8.2 Hz, 1H), 3.93 (s, 3H), 4.19-4.26 (m, 1H), 4.30 (d, J = 8.2 Hz, 1H), 4.47 (d, J = 10.4 Hz, 1H), 4.53 (d, J = 8.3 Hz, 1H), 5.16 (ddd, J = 14.9, 9.9, 1.7 Hz, 1H), 5.55 (ddd, J = 14.9, 6.5, 0.6 Hz, 1H) 7.20-7.25 (m, 4H), 7.30-7.60 (m, 6H). ^{13}C NMR δ: 17.4, 25.1, 48.6, 50.2, 50.5, 52.5, 53.6, 66.3, 66.9, 81.1, 123.4, 125.8, 127.4, 128.3, 129.3, 129.8, 131.7, 133.8, 138.9, 170.6, 173.7, 174.8, 175.1, 176.1. MS (EI) m/z: 513 (M$^+$, 6%), 455 (26), 454 (86), 341 (21), 340 (100), 193 (100), 282 (14), 281 (72), 228 (16), 115 (15). HRMS calculated for $C_{29}H_{27}N_3O_6$: 513.1900; found: 513.1896.

7,8-Diisobutyl 8a-methyl (3aS,4S,6R,7S,8S,8aS,8bR)-1,3-dioxo-2,6-diphenyl-4-[(E)-prop-1-en-1-yl]octahydropyrrolo[3,4-a]-pyrrolizine-7,8,8a(6H)-tricarboxylate (endo-18): The representative procedure was followed by using proline ester derivative *endo*-**14** (0.1 mmol, 40.5 mg). The desired product was obtained as colorless prisms (42.9 mg, 68% yield), mp 132-135 ºC (Et$_2$O), $[\alpha]_D^{26}$ = +4.1 (*c* 1.0, CHCl$_3$), IR (neat)

ν_{max}: 2960, 1381, 1223, 1178, 748 cm^{-1}. ^{1}H NMR δ: 0.77 (dd, J = 6.7, 2.4 Hz, 6H), 0.92 (d, J = 6.7 Hz, 6H), 1.61 (dt, J = 6.5, 1.8 Hz, 1H), 1.62 (hept, J = 6.7 Hz, 1H), 1.97 (hept, J = 6.7 Hz, 1H), 3.18 (dd, J = 10.6, 6.6 Hz, 1H), 3.49 (dd, J = 10.6, 6.6 Hz, 1H), 3.65 (d, J = 10.6 Hz, 1H), 3.73 (dd, J = 10.6, 8.4 Hz, 1H), 3.95 (dd, J = 12.2, 10.9 Hz, 1H), 3.91 (s, 3H), 3.95 (dd, J = 10.4, 6.7 Hz, 1H), 4.06 (dd, J = 10.4, 6.7 Hz, 1H), 4.31 (ddt, J = 8.4, 4.7, 1.9 Hz, 1H), 4.64 (d, J = 10.9 Hz, 1H), 4.77 (d, J = 12.2 Hz, 1H), 5.40 (ddq, J = 15.5, 4.7, 1.5 Hz, 1H), 5.95 (dqd, J = 14.9, 6.5, 1.9 Hz, 1H), 7.17-7.51 (m, 10H). ^{13}C NMR δ: 18.1, 19.0, 19.1, 19.2, 27.4, 27.6, 49.9, 50.1, 50.9, 51.0, 53.5, 63.2, 66.6, 71.3, 72.0, 80.0, 126.2, 126.8, 127.7, 128.1, 128.6, 129.2, 131.0, 132.3, 140.9, 169.2, 169.9, 170.3, 173.8, 175.0. MS (EI) m/z: 630 (M$^+$, <1%), 572 (17), 571 (45), 498 (15), 497 (48), 396 (28), 395 (100), 369 (30), 367 (16), 356 (12), 222 (12). HRMS calculated for C$_{36}$H$_{42}$N$_2$O$_8$: 630.2941; found: 630.2942.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: Experimental details, characterization data, and NMR spectra for new compounds (PDF), computational data and X-RD analysis.

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