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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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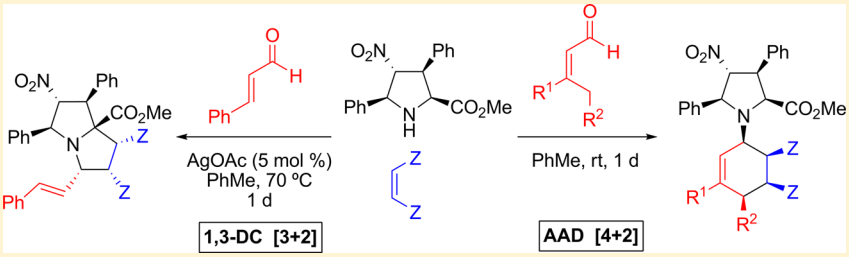
Supporting Information



ABSTRACT: Diastereoselective multicomponent reactions 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 carried out with the aim of explaining this different behavior between pyrrolidines with or without a nitro group, demonstrating the strong nitro-group-dependent periselectivity. The results of these computational studies also support the experimentally obtained absolute configuration of the final adducts.

INTRODUCTION

The 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. In particular, 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] 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 types 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 access to several hetero- and carbocycles as well as key structural cores of the natural product pumiliotoxin C.[11]

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,

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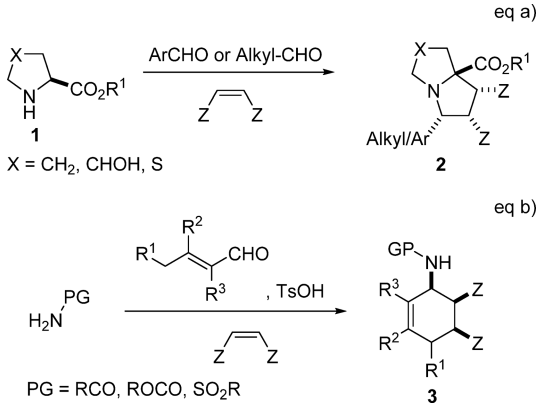
Scheme 1. (a) General Multicomponent 1,3-DC of Prolinates, Aldehydes, and Dipolarophiles Affording Pyrrolizidines 2 and (b) General Multicomponent [4 + 2] Cycloaddition of Amides−Aldehydes−Dienophiles (AAD Processes) Providing 3-Aminocyclohexenes 3



optically active polysubstituted nitroprolinates have emerged as promising therapeutic agents. For example, molecules **4** (Figure 1) are important inhibitors of $\alpha_4\beta_1$-integrin-mediated hepatic melanoma and in a murine model of colon carcinoma metastasis and have potent antiadhesive properties in several cancer cell lines.[13,14] Bicyclic heterocycles **5**, containing an atropane scaffold, have been found to be novel inhibitors of skin cancer.[15] Spiroxindoles **6** increased the mortality of zebrafish embryos,[16] while molecules **7** with a 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] The Michael-type addition of ketones to nitroalkenes was successfully organocatalyzed by *exo*-**8b** (X = H),[18] providing good to excellent diastereoselectivity 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 spiro compounds from chiral γ-lactams.[17,20,21] A family of enantiomerically enriched spironitroprolinates **10** has been obtained by our group from imino lactones and nitroalkenes which are currently being tested as anticancer agents.[22]

Continuing with our interest in the enantioselective synthesis of nitroprolinates and their synthetic applications, we describe here the periselectivity exihibited by enantiopure nitroprolinates toward 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% 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) with NMM acting as a 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, and proline derivatives[26,27] or diallylamine[27] have been reported. In the last case only nitrostyrenes were used as dienophiles.[27]

To study the scope of the 1,3-DC, cinnamaldehyde was selected as the 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, giving *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 cycloadduct **2e** being the major diastereoisomer (Table 1, entry 5). In the specific reaction with dialkyl acetylenedicarboxylates large quantities of 1,4-addition

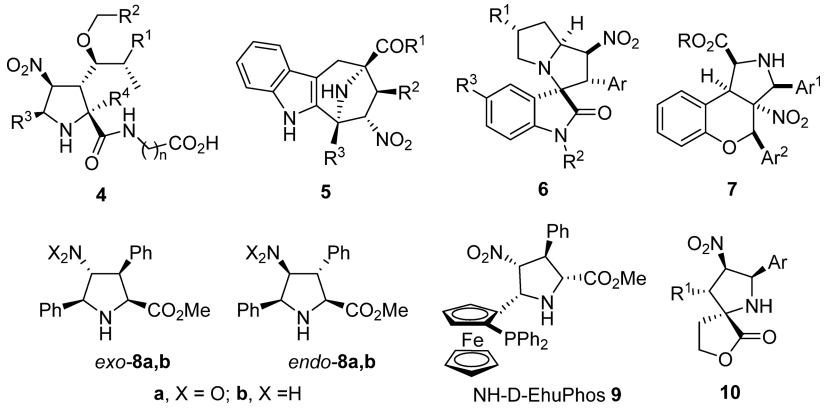


Figure 1. Interesting nitroprolinates with biological properties and with useful synthetic applications.

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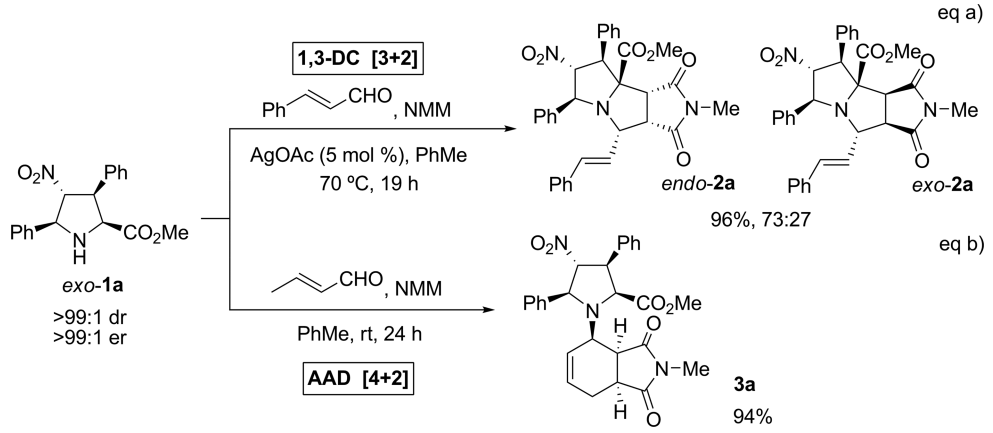
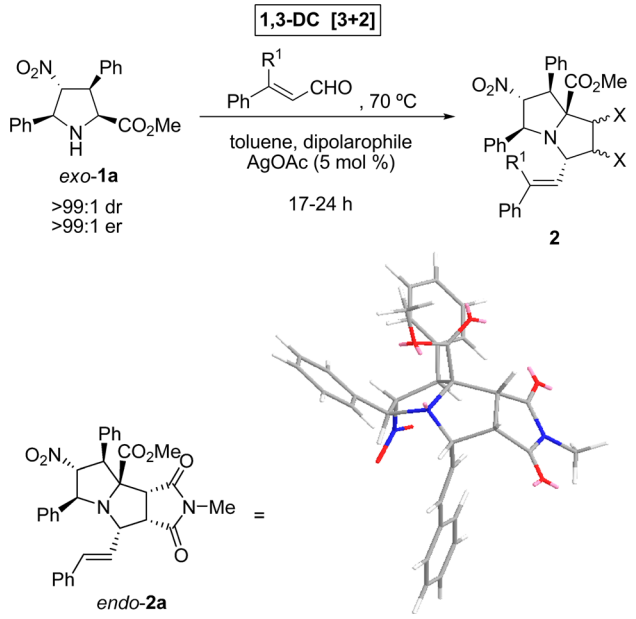
Scheme 2. Divergent Multicomponent Synthesis of Pyrrolizidines *endo*- and *exo*-2a via 1,3-DC or Polysubstituted Cyclohexenes 3a via AAD Process from Prolinate *exo*-1a, Aldehydes, and NMM



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



products of the nitroprolinate onto the electron-deficient alkyne were observed, furnishing the desired **2f** and **2g** products as unique diastereoisomers in modest yields (Table 1, entries 6 and 7).

β-Phenylcinnamaldehyde was also tested as a generator of the iminium salt in the presence of *N*-phenylmaleimide (NPM). The *endo*-cycloadduct **2h** was isolated in moderate yield with 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 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 on 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 the Experimental Section). In addition, these assignments are in perfect agreement with the absolute configuration revealed by X-ray diffraction analysis of the molecule *endo*-**2a**[28] (see the Supporting Information and Scheme 3).

The reactions performed with aliphatic or aromatic aldehydes, instead of *α,β*-unsaturated aldehydes, gave poor conversions of the expected pyrrolizidines. The employment of dipolarophiles such as nitroalkenes, vinyl sulfones, and chalcones under these conditions was not satisfactory.

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 $Cu(MeCN)_4PF_6$,[17,20] was not so useful as a 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 the pure racemic endo stereoisomer, in 72% yield (Scheme 4).

Scheme 4. Pyrrolizidines 2j,k Obtained from *endo*-Nitroprolinates 1 with Cinnamaldehyde and NPM

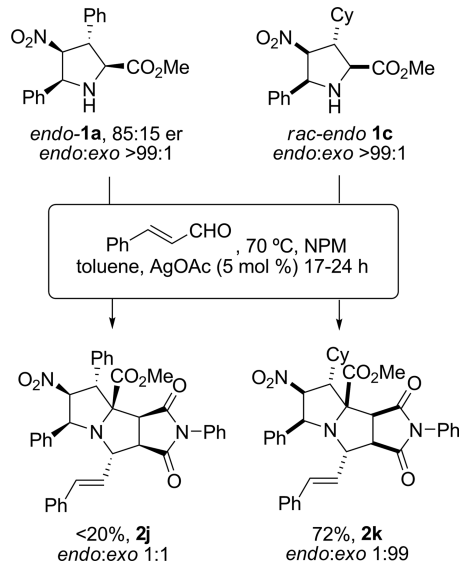


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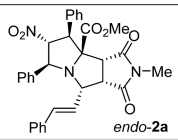
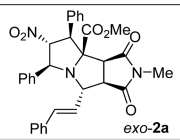
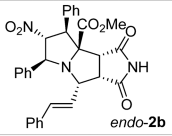
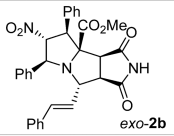
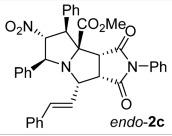
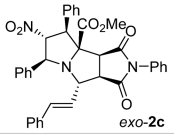
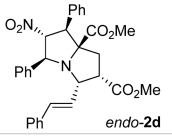
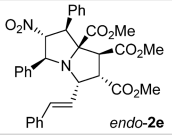
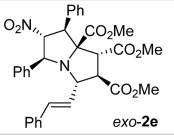
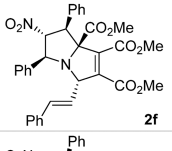
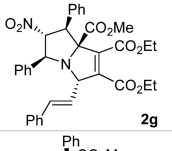
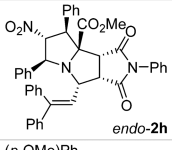
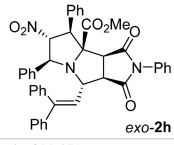
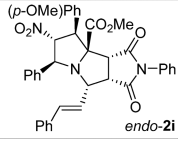
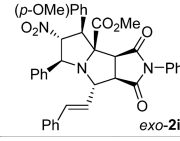
Table 1. Synthesis of Pyrrolizidines 2 via Multicomponent 1,3-DC from Enantiopure *exo*-1a and *exo*-1b

	Aldehyde		Product				
Entry	R^1	Dipolarophile	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
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**.

Yields represented in Scheme 4 agree with the overall yields obtained after purification as well as their corresponding dr values. In the reaction of nitroprolinate *endo*-**1a**, neither of the diastereoisomers *endo*- and *exo*-**2j** could be separated by flash chromatography (see the Experimental Section).

In these examples, as well as those described in entries 3 and 9 of Table 1, NPM approached the dipole with an exo orientation. The driving force that causes exo preference can be attributed to a lower destabilizing stereoelectronic interaction, mainly consisting of electrostatic repulsion between the nitro group of the dipole and the phenyl group of the dipolarophile, in comparison with the endo approach (see Figure 2 for an 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. Consequently, in this case the adduct *endo*-**2h** was the major diastereoisomer obtained.

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−e** (Scheme 5). 1,4-Benzoquinone afforded compound **3f** in 65% yield (determined by ^{1}H NMR spectra

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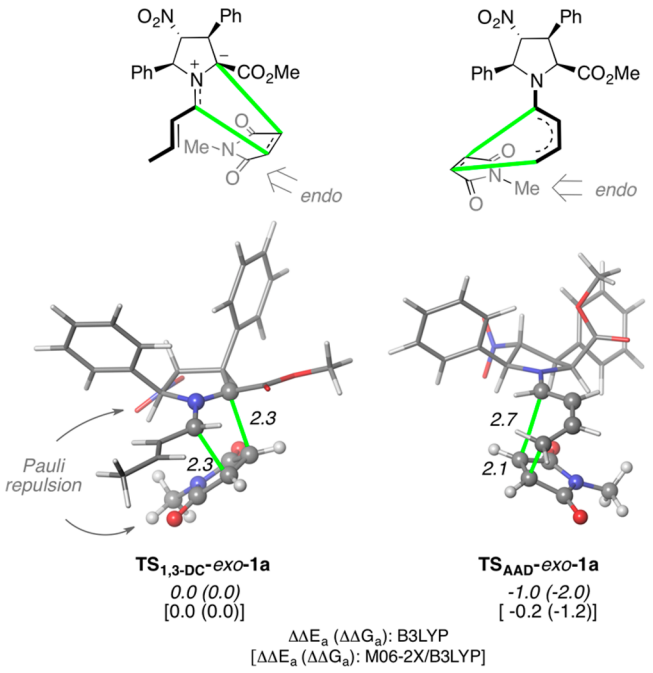

Figure 2. Relative energies, Gibbs free energies (in parentheses) and main geometrical features of the most stable transition structures associated with the 1,3-DC ($\mathbf{TS}_{1,3\text{-DC}}$-*exo*-**1a**) or multicomponent AAD ($\mathbf{TS}_{ADD}$-*exo*-**1a**) associated with the reaction of crotonaldehyde,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

of the crude product) at room temperature. Higher temperature (70 °C) 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,h** could not be purified by column chromatography due to partial decomposition or 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 NPM adducts **3i−k** in 62%, 89%, and 72% yields, respectively (Scheme 5). In all of 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 for compounds **3f,h** 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 shown in Scheme 5. The absolute configuration of new compound **3b** was unambiguously established by X-ray diffraction analysis[29] (see the Supporting Information and Scheme 5). For other molecules **3** complementary ^{1}H NMR analysis also confirmed the drawn structures depicted in Scheme 5.

Two nitroprolinates, *exo*-**1b** and *rac-endo*-**1c**, were tested as precursors in this AAD domino reaction with NPM and crotonaldehyde. The reaction of *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).

It is worth noting that no AAD multicomponent reaction was observed during the reaction of L-proline methyl ester **11** or proline ester derivatives **12−14**. In these cases, 1,3-DC occurred instead and the corresponding *endo*-pyrrolizidines **15−18** were formed in 61%, 69%, 67%, and 68% yields, respectively (Scheme 7).

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) on 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 and the pyrrolizidine synthesis via 1,3-DC.

The initial step in the proposed mechanism consists of 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 the presence of a base, **A** can evolve into the azomethine ylide **B** by abstraction of the hydrogen atom located at the α-position of the methoxycarbonyl group, which leads to pyrrolizidines **2** and **15−18** or to the dienamine intermediate **C** by abstraction of the hydrogen atom in the γ-position of crotonaldehyde, thus forming cyclohexenylpyrrolidines **3**.

According to the Fukui frontier molecular orbital (FMO) theory,[30] π4s + π2s cycloaddition reactions are mainly governed by symmetry-allowed $HOMO_{dipole/diene}-LUMO_{dipolarophile/dienophile}$ interactions. Within this framework, the small energy gap $\Delta E_{HOMO-LUMO}$ is related to high reactivity. Inspection of the reagent FMOs showed that the less stable azomethine ylides **B** seem to be more reactive than dienamines **C**, regardless of the proline derivative **1** used (see the Supporting Information). As a consequence of this reactivity−stability dichotomy, in which unstable reagents are the most reactive,[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−Hammett 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 concerned, our calculations show that the transition structure associated with the AAD multicomponent reaction ($\mathbf{TS}_{AAD}$-*exo*-**1a**) is 1.2 kcal mol^{-1} more stable than its 1,3-DC analogue $\mathbf{TS}_{1,3\text{-DC}}$-*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

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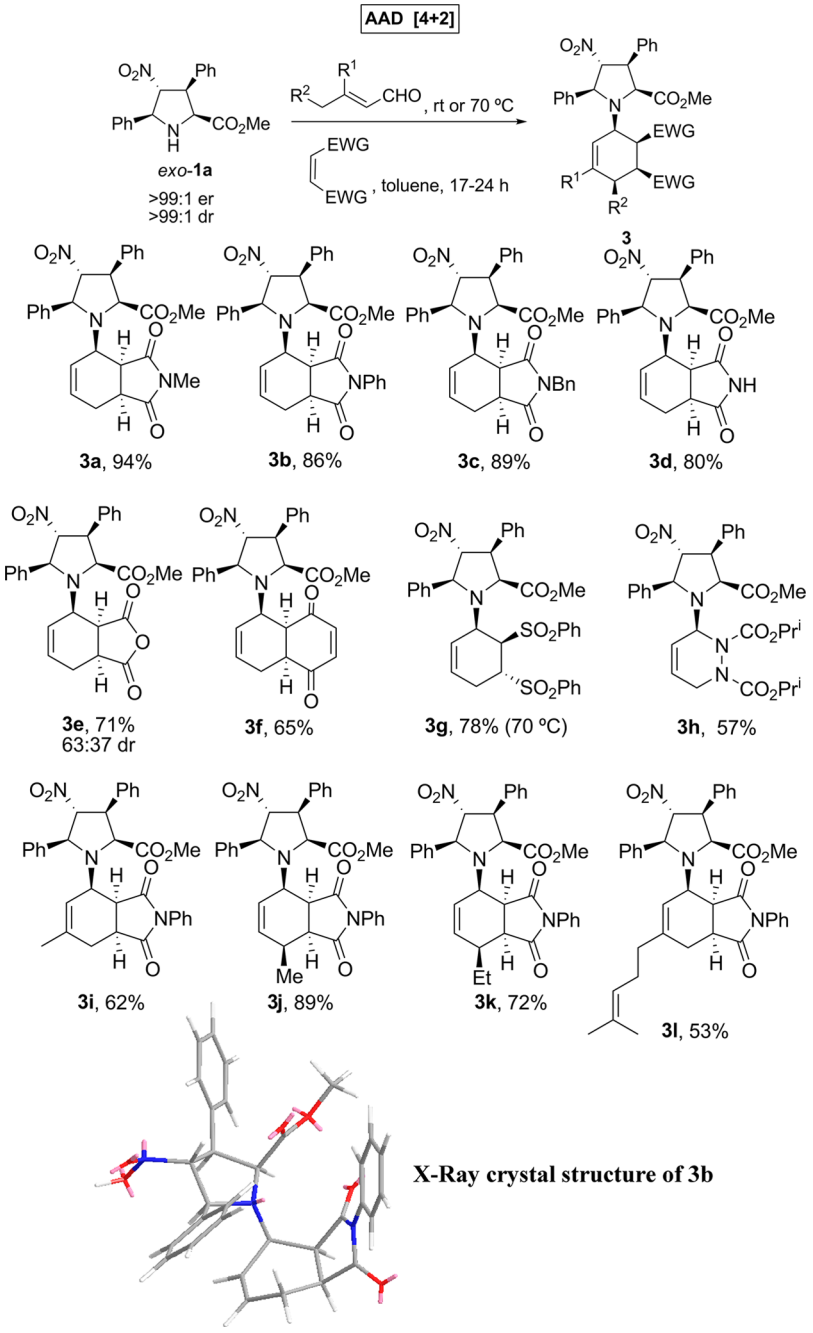
Scheme 5. Polyfunctionalized Cyclohexenes 3 Obtained from AAD Employing Nitropolinate *exo*-1a, α,β-Unsaturated Aldehydes with Hydrogen Atoms at the γ-Position and Dienophiles, and X-ray Diffraction Analysis of Compound 3b



transition structures TS_{AAD} associated with formation of cyclohexenylpyrrolidines **3** (especially those comparing the endo and the exo approaches) show a theoretical dr of ca. 99:1, in perfect agreement with the experimental results (see the Supporting Information).

Analysis of the geometries depicted in Figure 2 also supports a diastereofacial bias in the highly substituted nitroproline *exo*-**1a** derived transition state, where substituents in positions 2, 3, and 5 effectively block one face of the azomethine ylide or the aminodiene intermediate. Therefore, in $TS_{1,3\text{-DC}}$-*exo*-**1a** the dipolarophile has to approach 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 that which it adopts in the transition state structure, making the 1,3-DC energetically inaccessible, and thus converting the low-distorted AAD reaction the preferred process (see the distortion/interaction analysis[33] in the Supporting Information). With regard to these Pauli repulsions, it is plausible to assume that they are responsible for the favorable exo approach of NPM in the course of 1,3-DCs.

On the other hand, the employment of proline derivatives **11**–**14** (Scheme 7) implies a change in the periselectivity of the reaction. In this example, preferential formation of pyrrolizidine **15** was observed, $TS_{1,3\text{-DC}}$ (associated with the 1,3-DC) being ca. 3 kcal mol^{-1} more stable than its TS_{AAD} counterpart, in good agreement with the periselectivity observed experimen-

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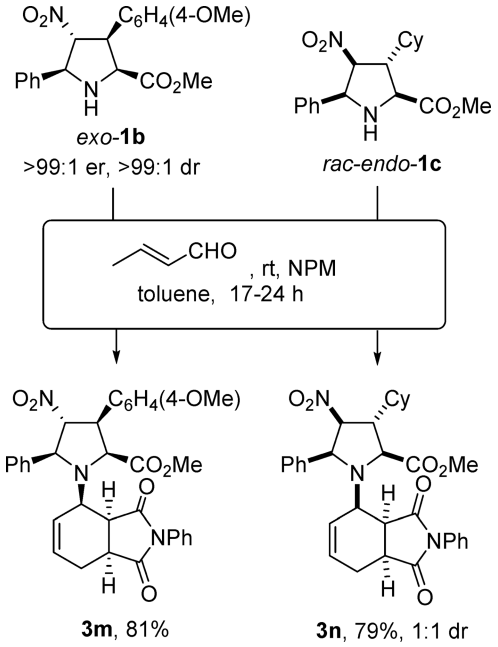
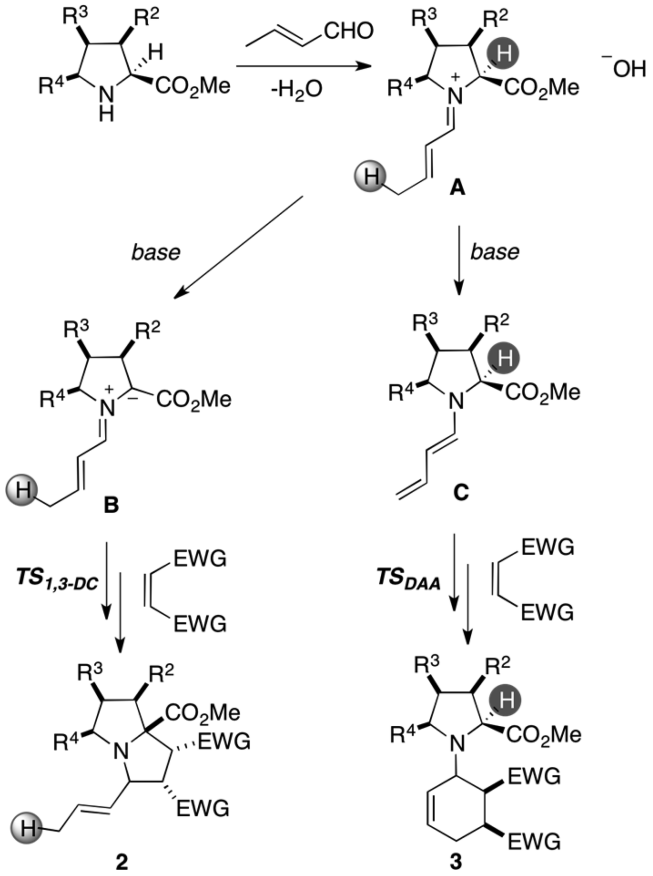
Scheme 6. Products 3m,n Obtained from an AAD Sequence Employing Different *exo*- and *endo*-Nitroprolinates with Crotonaldehyde and NPM



Scheme 8. General Scheme of the Reaction of Prolinates, Aldehydes, and Dipolarophiles Affording Pyrrolizidines 2 or Cyclohexenylpyrrolidines 3[a]

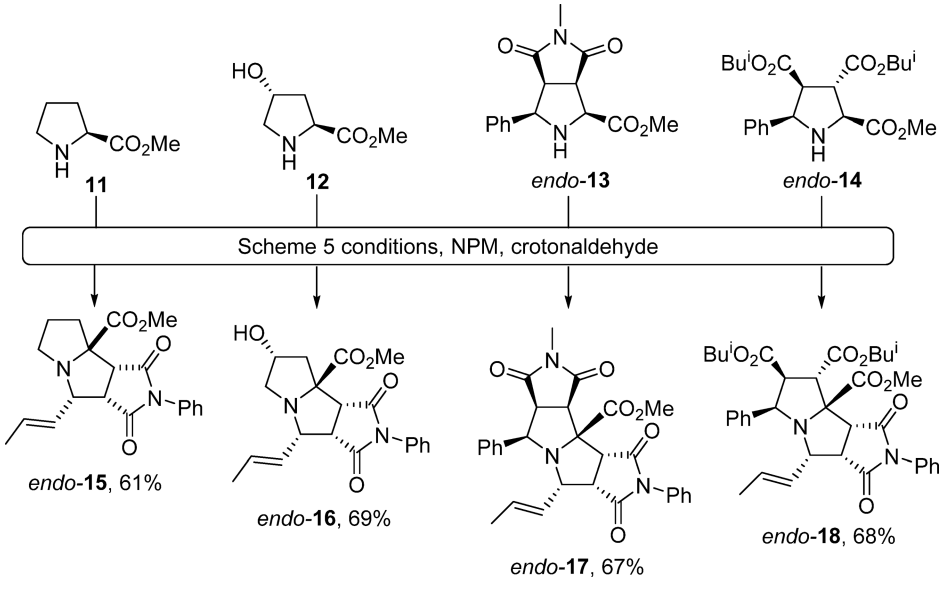


[a]Acidic positions are highlighted.

tally (Figure 3). A detailed inspection of the geometries shows that generation of reactive azomethine ylides **B** (Scheme 8) forces the pyrrolidine ring (and consequently 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 a 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. However, this increment never generates a $TS_{1,3\text{-DC}}$ with energy higher than that of the corresponding TS_{AAD} species (14.4 and 18.7 kcal mol^{-1}, respectively). Thus, a strong preference for the 1,3-DC is observed.

However, in dienamine intermediates (Figure 4) the pyrrolidine ring has a twist conformation where most of the

Scheme 7. Products *endo*-15−18 Obtained from 1,3-DC Employing Different Methyl Prolinates with Crotonaldehyde and NPM



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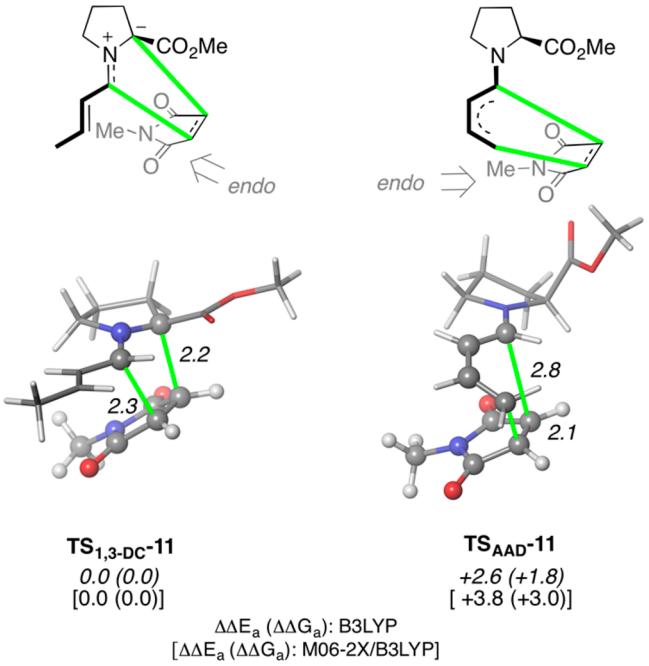

Figure 3. Relative Gibbs free energies and main geometrical features of the most stable transition structures associated with the 1,3-DC ($\mathbf{TS}_{1,3\text{-DC}}$-**11**) or multicomponent AAD ($\mathbf{TS}_{AAD}$-**11**) associated with the reaction of crotonaldehyde, NMM, and (B) proline **11**.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

substituents are placed in an equatorial position. In both of these examples, the steric hindrance is considerably lower than in the former $\mathbf{TS}_{AAD}$-**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 at the less hindered face. Therefore, in this case, 1,3-DC was preferred over a multicomponent AAD process, as was observed for L-proline methyl ester **11**. Consequently, 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 way similar to that for *exo*-**1a**, the steric requirements of the methoxycarbonyl groups are smaller than those of 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 ($\mathbf{TS}_{1,3\text{-DC}}$-*endo*-**14**) was found to be 3.6 kcal mol^{-1} more stable than that of its AAD counterpart ($\mathbf{TS}_{AAD}$-*endo*-**14**). Preferential formations of pyrrolizidines **15**–**18** are theoretically assessed when **11**–**14** are used as starting materials.

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 absence of hydrogen atoms at the γ-position of the aldehyde determines the periselectivity toward 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 *endo*-3-aminocyclohexenes. On the

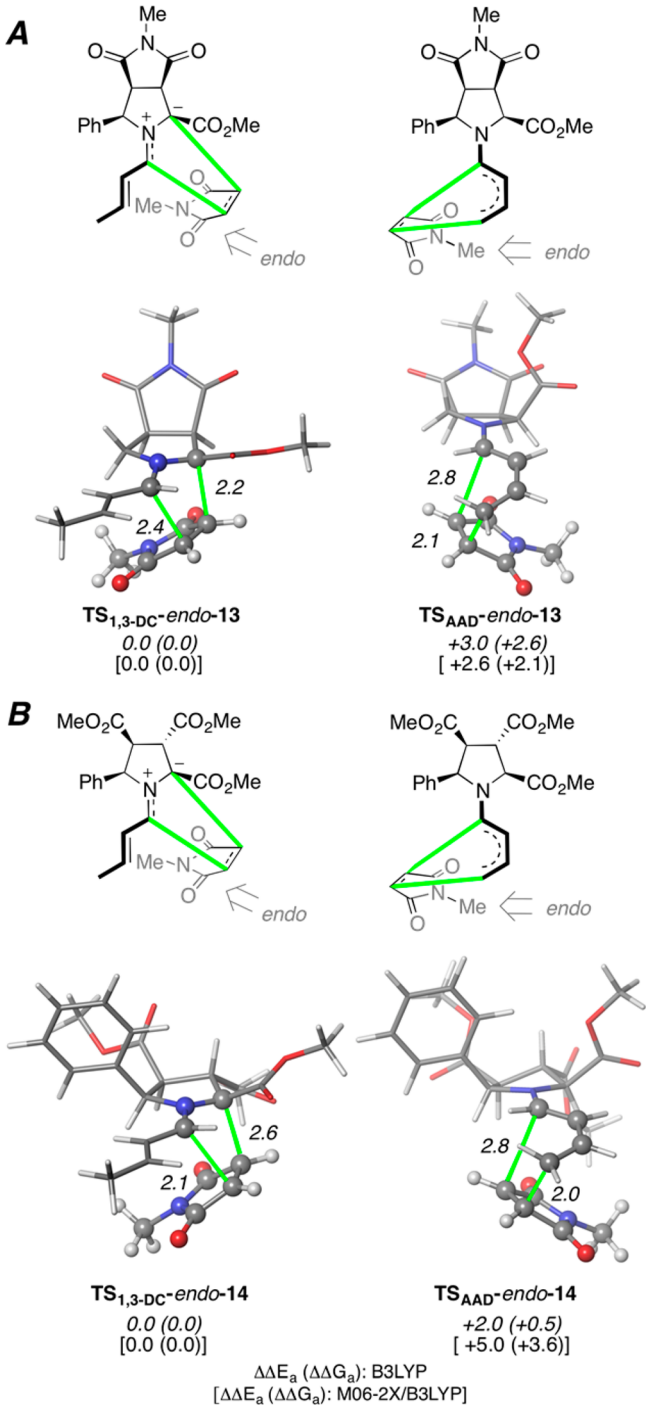

Figure 4. Relative Gibbs free energies and main geometrical features of the most stable transition structures associated with the 1,3-DC ($\mathbf{TS}_{1,3\text{-DC}}$-*endo*-**13** and $\mathbf{TS}_{1,3\text{-DC}}$-*endo*-**14**) or multicomponent AAD ($\mathbf{TS}_{AAD}$-*endo*-**13** and $\mathbf{TS}_{AAD}$-*endo*-**14**) associated with the reaction of crotonaldehyde, NMM, and (A) *endo*-**13** or (B) *endo*-**14**. See the caption of Figure 2 for further details.

basis of the DFT calculations presented here, it was supported that azomethine ylides derived from proline derivatives and crotonaldehyde are in general more reactive than their dienamine counterparts, the 1,3-DC being preferred over the AAD reaction. Only in the case of highly hindered azomethine ylides, such as that derived from *exo*-**1a**, is 1,3-DC hindered due to the huge energy required to distort the reagents into the transition structure geometry. Therefore, the less reactive

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dienamine takes importance, the AAD pathway being the only one energetically accessible. Evaluations 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 distilled prior to use. Analytical TLC was performed on Schleicher & Schuell F1400/LS 254 silica gel plates, and the spots were visualized under UV light (λ 254 nm). Flash chromatography was carried out on hand-packed 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 PerkinElmer 341 polarimeter with a thermally jacketed 5 cm cell at approximately 25 °C, 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 instrument) are listed, and wavenumbers are given in cm^{-1}. NMR spectra were obtained using a Bruker AC-300 or AC-400 spectrometer and were recorded at 300 or 400 MHz for ^1H 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 instrument 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 instrument.

Computational Methods. All of 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 geometries similar to those for 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 of 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 created 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−k. To a stirred solution of the nitroprolinate **1** (0.1 mmol) in toluene (1 mL) were added the aldehyde (0.1 mmol) and the dipolarophile (0.1 mmol). Then 5 mol % of AgOAc (0.005 mmol, 0.84 mg) was added and the reaction mixture was stirred overnight at 70 °C in the dark. Then the reaction mixture 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_2O), $[\alpha]_D^{28}$ = +160.3 (c 1.0, $CHCl_3$). IR (neat) ν_{max}: 1742, 1697, 1552, 1208, 1037, 968 cm^{-1}. ^1H 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 $C_{32}H_{29}N_3O_6$, 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_2O), $[\alpha]_D^{29}$ = +76.1 (c 0.5, $CHCl_3$). IR (neat) ν_{max}: 1737, 1700, 1551, 1434, 1372, 1279, 1131, 1084, 968 cm^{-1}. ^1H 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 °C (Et_2O), $[\alpha]_D^{26}$ = +179.2 (c 1.0, $CHCl_3$). IR (neat) ν_{max}: 1711, 1554, 1356, 1192, 750 cm^{-1}. ^1H 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 °C (Et_2O), $[\alpha]_D^{26}$ = +81.3 (c 1.0, $CHCl_3$). IR (neat) ν_{max}: 1712, 1552, 1340, 1180, 737 cm^{-1}. ^1H 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 °C (Et_2O), $[\alpha]_D^{24}$ = −31.5 (c 0.6, $CHCl_3$). IR (neat) ν_{max}:

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1707, 1552, 1387, 1192, 742 cm^{-1}. ^1H 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 °C (Et_2O), $[\alpha]_D^{26}$ = −131.2 (c 1.0, $CHCl_3$). IR (neat) ν_{max}: 1707, 1549, 1379, 1184, 739 cm^{-1}. ^1H 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 $C_{37}H_{31}N_2O_4$ [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 a 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}. ^1H 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 $C_{31}H_{30}N_2O_6$, 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 dimethyl fumarate (0.1 mmol, 14.4 mg). The desired product was obtained as a sticky colorless oil (27.9 mg, 48% yield): $[\alpha]_D^{26}$ = +80.9 (c 0.8, $CHCl_3$). IR (neat) ν_{max}: 1717, 1700, 1549, 1251 cm^{-1}. ^1H 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 $C_{33}H_{32}N_2O_8$, 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 a sticky colorless oil (15.1 mg, 26% yield): $[\alpha]_D^{26}$ = +31.8 (c 0.5, $CHCl_3$). IR (neat) ν_{max}: 1712, 1699, 1547, 1250 cm^{-1}. ^1H 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 $C_{33}H_{32}N_2O_8$, 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 a sticky yellow oil (17.8 mg, 31% yield): $[\alpha]_D^{27}$ = +131.2 (c 1.0, $CHCl_3$). IR (neat) ν_{max}: 1734, 1555, 1435, 1265, 1227 cm^{-1}. ^1H 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 $C_{33}H_{30}N_2O_8$, 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 °C (Et_2O), $[\alpha]_D^{28}$ = +141.9 (c 0.7, $CHCl_3$). IR (neat) ν_{max}: 1744, 1722, 1555, 1286, 1270, 1227 cm^{-1}. ^1H 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 $C_{35}H_{34}N_2O_8$, 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 °C (Et_2O), $[\alpha]_D^{27}$ = +25.1 (c 1.0, $CHCl_3$). IR (neat) ν_{max}: 1710, 1552, 1497, 1372, 1265, 1215 cm^{-1}. ^1H 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 $C_{43}H_{35}N_2O_4$ [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 °C (Et_2O), $[\alpha]_D^{26}$ = +66.9 (c 0.5, $CHCl_3$). IR (neat) ν_{max}: 1711, 1552, 1495, 1375, 1259, 1182, 1028 cm^{-1}. ^1H 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),

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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 °C (Et_2O), $[\alpha]_D^{27}$ = −48.3 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 1711, 1552, 1517, 1496, 1373, 1254, 1180, 735 cm^{-1}. ^1H 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 °C (Et_2O), $[\alpha]_D^{26}$ = −100.4 (*c* 0.9, $CHCl_3$). IR (neat) ν_{max}: 1710, 1554, 1514, 1495, 1377, 1252, 1178, 1032, 756 cm^{-1}. ^1H 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-Cyclohexyl-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 a sticky yellow oil (45.0 mg, 72% yield). IR (neat) ν_{max}: 1712, 1550, 1371, 1184, 908, 729 cm^{-1}. ^1H 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−n. To a stirred solution of the nitroprolinate **1** (0.1 mmol) in toluene (1 mL) were added the aldehyde (0.1 mmol) and the dienophile (0.1 mmol). 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_2O), $[\alpha]_D^{26}$ = 95.5 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 1739, 1697, 1551, 1436, 1200, 1155 cm^{-1}. ^1H 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 $C_{27}H_{27}N_2O_4$ [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_2O), $[\alpha]_D^{26}$ = +40.2 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 1700, 1555, 1387 cm^{-1}. ^1H 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 °C (Et_2O), $[\alpha]_D^{27}$ = +63.7 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 1738, 1697, 1551, 1398, 1350, 1201, 1159 cm^{-1}. ^1H 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 °C (Et_2O), $[\alpha]_D^{26}$ = +90.5 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 1699, 1551, 1353, 1199, 1162 cm^{-1}. ^1H 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

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(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 $C_{26}H_{25}N_2O_4$ [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 a sticky yellow oil (33.9 mg, 71% yield). Data for the major isomer are as follows. IR (neat) ν_{max}: 1774, 1739, 1552, 1203, 910, 731 cm^{-1}. ^1H 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_2Me], 370.1443; found, 370.1451.

*(2S,3S,4R,5S)-1-((1R,5R,6R)-5,6-Bis(phenylsulfonyl)cyclohex-2-en-1-yl)-2-((methylperoxy)-λ²-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 °C (Et_2O). IR (neat) ν_{max}: 1737, 1551, 1447, 1308, 1204, 1146, 1081, 756 cm^{-1}. ^1H NMR [mixture of endo:exo (1:0.5)]: δ 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 [mixture of endo:*exo* (1:0.5), data of the major endo diastereoisomer]: δ 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_2O), $[\alpha]_D^{29}$ = +73.1 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 1746, 1705, 1548, 1500, 1384 cm^{-1}. ^1H 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 $C_{33}H_{31}N_3O_6$, 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_2O), $[\alpha]_D^{26}$ = +104.3 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 1699, 1552, 1385, 1192, 1032, 762 cm^{-1}. ^1H 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 °C (Et_2O), $[\alpha]_D^{26}$ = +84.3 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 1699, 1552, 1385, 1188, 1030, 758 cm^{-1}. ^1H 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 °C (Et_2O), $[\alpha]_D^{24}$ = +34.3 (*c* 0.6, $CHCl_3$). IR (neat) ν_{max}: 1743, 1703, 1549, 1375, 1163, 750 cm^{-1}. ^1H 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 $C_{38}H_{39}N_2O_4$ [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 °C (Et_2O), $[\alpha]_D^{25}$ = +86.3 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 1745, 1702, 1550, 1517, 1388, 1254, 1156, 1024, 796, 761 cm^{-1}. ^1H 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

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(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 °C (Et_2O). IR (neat) ν_{max}: 1705, 1551, 1380, 1166 cm^{-1}. ^1H NMR [mixture of diastereoisomers (1:1)]: δ 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 [mixture of diastereoisomers (1:1)]: δ 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 prolinates **11**−**14** (0.1 mmol) in toluene (1 mL) were added crotonaldehyde (0.1 mmol, 8.3 μL) and *N*-phenylmaleimide (0.1 mmol, 17.3 mg). 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 a sticky yellow oil (21.6 mg, 61% yield). IR (neat) ν_{max}: 1707, 1498, 1376, 1215, 1176, 967, 733 cm^{-1}. ^1H 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 a 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}. ^1H 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 °C (Et_2O), $[\alpha]_D^{25}$ = +96.1 (*c* 0.9, $CHCl_3$). IR (neat) ν_{max}: 1705, 1436, 1379, 1177, 1060, 963, 733 cm^{-1}. ^1H 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 °C (Et_2O), $[\alpha]_D^{26}$ = +4.1 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 2960, 1381, 1223, 1178, 748 cm^{-1}. ^1H 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 $C_{36}H_{42}N_2O_8$, 630.2941; found, 630.2942.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00903.

Experimental details, characterization data, and NMR spectra for new compounds, crystallographic data, and computational data (PDF)
Crystallographic data (CIF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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