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Three-Component Reactions with (*S*)-Methyl Pyroglutamate: An Efficient Way to Diversely Substituted Asymmetric Amidocyclohexenes

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Abstract: Chiral *N*-dienyl lactams are crucial building blocks for the synthesis of complex organic compounds. However, their generation is rather challenging. This paper reports the novel one-pot reaction of (*S*)-methyl pyroglutamate as the **a**mide component with different **a**ldehydes and **d**ienophiles (AAD reaction) to give novel chiral 1-amido-2-cyclohexenes. The corresponding *N*-dienyl lactams generated in situ undergo subsequent Diels–Alder reactions in good yield and diastereoselectivity. The scope and limitations of the three-component protocol were investigated. X-ray and NMR spectroscopic analysis of the products as well as DFT calculations of the intermediates were also performed to explain the observed stereoselectivity and structural features.

Keywords: chiral dienamides · diastereoselectivity · Diels–Alder reactions · multicomponent reactions · pyroglutamate

Introduction

Multicomponent reactions (MCRs) offer significant advantages over stepwise procedures,[1] especially with respect to environmental sustainability, practicability, and atom efficiency.[2] Compared to sequential reactions, the most evident benefit of MCRs lies in the inherent formation of several bonds in one operation without the need to isolate the intermediates, change the reaction conditions, or add any further reagents. Historically significant examples of MCRs are the Strecker reaction,[3] the Hantzsch pyrrole synthesis,[4,5] the Hantzsch dihydropyridine synthesis,[5,6] the Biginelli synthesis of dihydropyrimidines,[5,7] the Mannich reaction,[8] and the Ugi MCR.[9] These and other prominent reactions are well-established and provide a basis for the tremendous richness of multicomponent chemistry. Clearly, MCRs nowadays constitute one of the most effective tools in organic synthesis. Nevertheless, the demand for the development of more diversified and especially stereoselective MCRs to establish novel substance libraries still exists.

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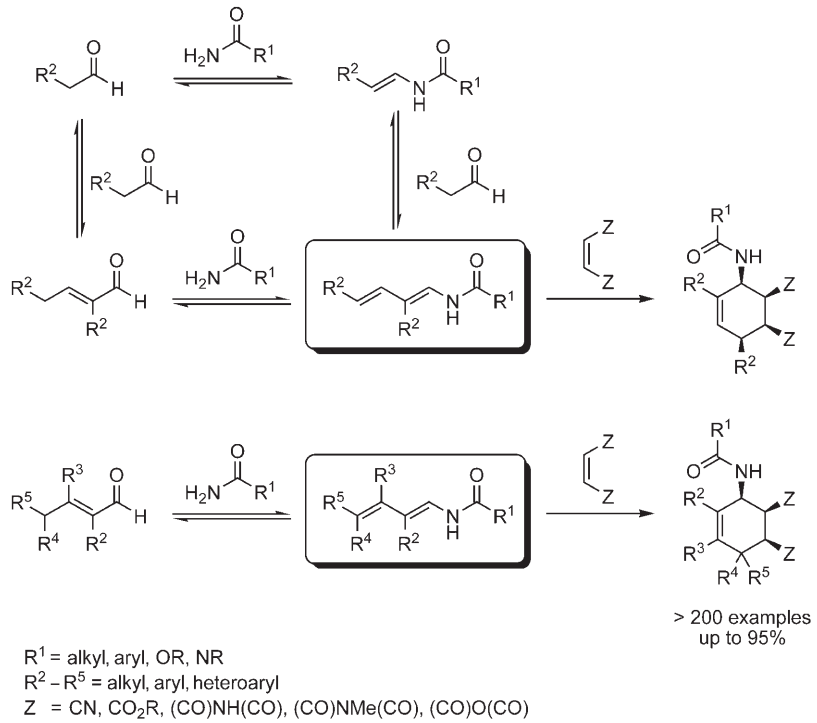
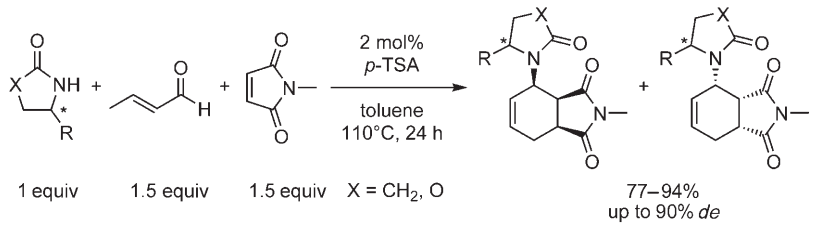
A few years ago, we discovered a new multicomponent methodology in which **a**mides and **a**ldehydes react with **d**ienophiles (AAD reaction) to give a large variety of 1-acylamino-2-cyclohexene derivatives with unprecedented efficiency.[10–13] The AAD reaction involves 1-(*N*-acylamino)-1,3-butadienes as key intermediates, which are generated in the initial condensation step and subsequently trapped by dienophiles in a Diels–Alder reaction (Scheme 1).

By utilizing simple aliphatic and aromatic aldehydes, the substitution of the 1,3-diene backbone is limited to the 2- and 4-positions only, because of the incorporation of two identical aldehyde molecules (Scheme 1, top). However, employment of α,β-unsaturated aldehydes, which presumably constitute an integral component of the overall reaction mechanism, affords 1-(*N*-acylamino)-1,3-butadiene building blocks with four potential substitution centers at the 1,3-butadiene backbone and, hence, significantly increases the substrate diversity (Scheme 1, bottom).[11] A special feature of the AAD reaction is the tolerance of a large variety of amides.[12] The importance of Diels–Alder chemistry with respect to natural-product synthesis has recently directed our attention to the development of stereoselective variants of the AAD reaction. Owing to the selective *endo* addition of the dienophiles throughout the Diels–Alder step, diastereoselective induction is easily achieved by differentiation of the two faces of the 1,3-diene, assuming that the dienophile approaches from the less-hindered side.

While studying the reaction of crotonaldehyde and *N*-methyl maleimide with different chiral amides (Scheme 2),



Scheme 1. General reaction scheme of the **a**ldehyde–**a**mide–**d**ienophile multicomponent reaction (AAD MCR).



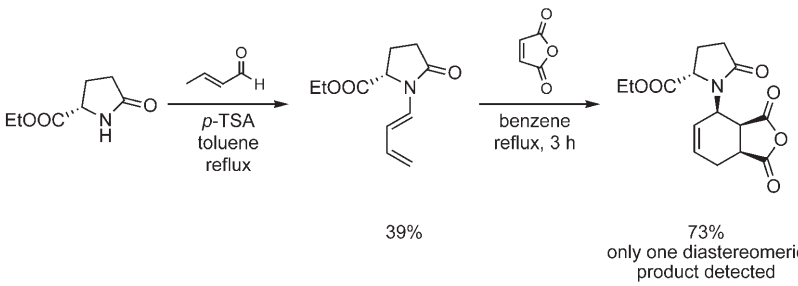
Scheme 2. Diastereoselective AAD reaction of crotonaldehyde and *N*-methyl maleimide in combination with oxazolidinones and pyrrolidinones, respectively. *p*-TSA = *p*-toluenesulfonic acid.

we discovered that phenyl-substituted oxazolidinone (R = Ph, X = O) provided the corresponding AAD product with a diastereomeric excess of 90%.[14]

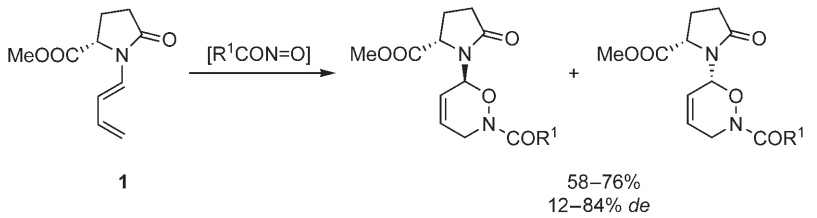
To discover the scope and limitations of diastereoselective AAD reactions, we were interested in whether different substitution patterns on aldehydes and dienophiles affected the stereochemical outcome. Here, we became attracted by the use of (*S*)-methyl pyroglutamate as the chiral amide component because of its low cost and easy availability. Moreover, pyroglutamates have in the past proved to be versatile and convenient building blocks for asymmetric synthesis.[15] The first application of pyroglutamates as an auxiliary in a sequential condensation–Diels–Alder sequence was reported by Smith and co-workers (Scheme 3).[16]

In 1991, Streith and co-workers treated *N*-dienyl pyroglutamate **1** with acylnitroso dienophiles in Diels–Alder reactions (Scheme 4).[17] Depending on the substitution pattern at the dienophiles, the *de* achieved ranged from 12 to 84%. Optimization experiments revealed that the best results were obtained in methanol at low temperatures (−78°C to room temperature). Later, their group also investigated the influence of the pyroglutamic ester moiety. They showed that asymmetric induction increased with the size of the ester group. At 0°C with the same acylnitroso dienophile, the *N*-dienyl lactam bearing the methyl ester delivered 46% *de*, whereas the corresponding *tert*-butyl ester provided 68% *de*.[18] The same group also studied double asymmetric induction by employing both enantiomerically pure *N*-dienyl pyroglutamates and chiral acylnitroso dienophiles. Here, up to 96% *de* was reached in one example.[19]

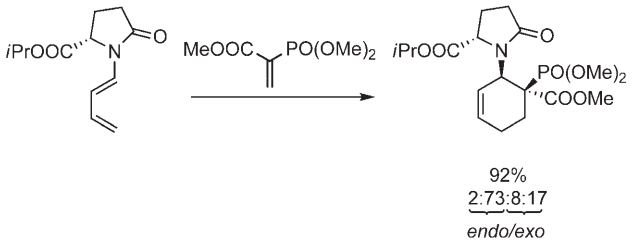
In the course of their studies on aminophosphonic derivatives, Robiette and Marchand-Brynaert investigated the application of *iso*-propyl *N*-dienyl pyroglutamate in [4+2] cycloadditions.[20] In contrast to the hetero-Diels–Alder chemistry of Streith and co-workers with highly reactive nitroso dienophiles, this group reported on the conversion of the less-reactive "carbonic" phosphono acrylates with *N*-dienyllactams (Scheme 5). Unfortunately, the cycloaddition was not very *endo*/*exo*-selective; hence, four isomeric cyclo-



Scheme 3. The first utilization of an *N*-dienyl pyroglutamate in a Diels–Alder reaction.



Scheme 4. *N*-dienyl pyroglutamate **1** in an asymmetric hetero-Diels–Alder reaction.



Scheme 5. Application of an *N*-dienyl pyroglutamate in a Diels–Alder reaction with phosphono acrylates.

adducts were formed. The configuration of the main diastereomer was determined as depicted in Scheme 5 by X-ray diffraction, NMR spectroscopy, and DFT calculations.

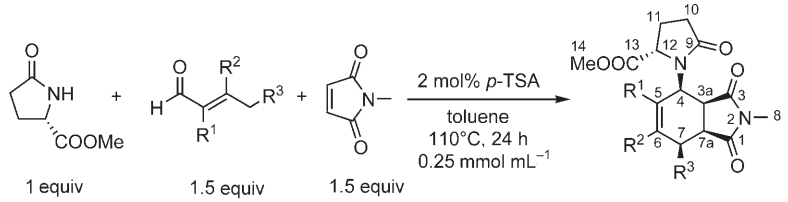
All of the aforementioned strategies represent rather specialized multistep procedures. Even though good yields and diastereoselectivities were achieved, long reaction times (up to 72 h), low temperatures (down to −78 °C), and the formation of up to four isomers lower their synthetic value. Very recently, asymmetric Diels–Alder-based MCRs and domino reactions have been nicely reviewed by Ramón and Yus[21] as well as Pellissier,[22] but to the best of our knowledge generation of chiral *N*-dienyl pyroglutamates in situ has not been reported in the literature so far. Herein, we wish to report on the utilization of commercially available, inexpensive (*S*)-methyl pyroglutamate as the chiral amide component in highly selective and straightforward MCRs to give 1-amido-2-cyclohexene derivatives.

Results and Discussion

To begin, we wanted to know how substituents along the cyclohexene backbone change the stereochemical outcome of this multicomponent procedure. To observe differences in *de* more distinctively, we decided to utilize (*S*)-methyl pyroglutamate, which gives moderate diastereoselectivity in the reaction with crotonaldehyde and *N*-methyl maleimide (77% yield, 74% *de*).[14] Next, we employed α- and β-methyl crotonaldehyde as well as pentenal in combination with *N*-methyl maleimide and (*S*)-methyl pyroglutamate (Table 1). For determination of yields, preparative experiments were performed on a 3.0-mmol scale. The *de* was determined from the crude reaction mixtures. Therefore, reactions on a smaller scale (0.5 mmol) were run, and the crude reaction mixtures were subjected to ^{13}C NMR spectroscopic (inverse gated decoupling = IG) analysis, which allows the integration of the carbon signals.

As shown in Table 1, in all cases the cycloadducts were obtained in moderate to good yields (48–82%). The assignation of the stereoselectivities for the AAD products **2** to **5** was challenging because of their similar physical properties. For compound **2**, the minor diastereomer was obtained in a mixture with the corresponding major diastereomer. In the case of derivatives **4** and **5**, the major stereoisomers **4a** and **5a**, respectively, were isolated, whereas the NMR data of the minor isomers **4b** and **5b** were extracted from the crude reaction mixtures. On the basis of NMR spectroscopy of both the isolated fractions and the crude reaction mixtures, the diastereoselectivities for compounds **2**, **4**, and **5** were de-

Table 1. (*S*)-Methyl pyroglutamate and *N*-methyl maleimide in combination with different aldehyde components in the diastereoselective AAD reaction.



Compound	2	3	4	5
Yield [%],[a] *de* [%][b]	77, 74	48[c]	82, 67	78, 82

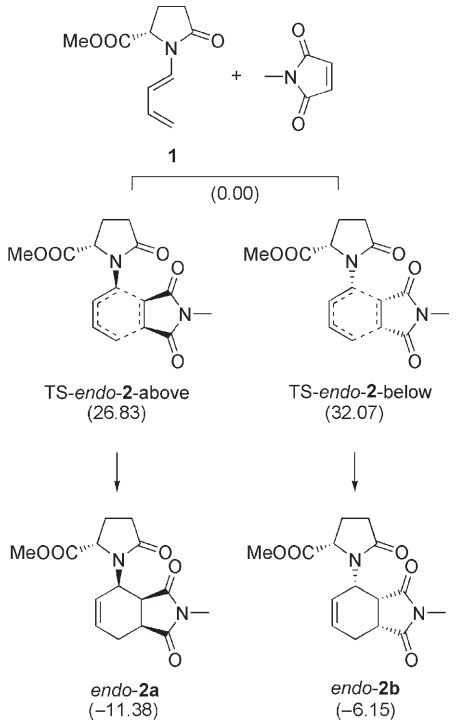
[a] Yield of isolated product. [b] Diastereomeric excess determined by ^{13}C NMR spectroscopy (inverse gated decoupling = IG) of the crude reaction mixture. [c] Reaction temperature: 160 °C.

termined from the crude reaction mixtures (67–82% *de*). Notably, a higher reaction temperature (160°C) was required for the preparation of pyroglutamate derivative **3**, which was obtained in 48% yield. However, it was not possible in this case to determine an appropriate *de* value from the crude reaction mixture.

Clearly, the position of a substituent along the dienamide backbone generated in situ does not have a distinctive impact on the stereoselectivity of our procedure. However, for a more-detailed insight, we also performed DFT calculations on the different pyroglutamate derivatives (Scheme 6). The computational details and strategies as well as the calculated energy data at various levels of theory are given in the Experimental Section and the Supporting Information.

In previous computations of stereoselective Diels–Alder reactions of substituted oxazolidinone derivatives, the diastereoselectivity was found to originate from a kinetically controlled process through steric discrimination between the substituent at the stereocenter and the dienophile.[14] In this paper, we used the same procedure to compute the diastereoselectivity of the substituted 1,3-butadienes shown in Scheme 6. As diastereoselectivity relies on the relative position of the dienophile to the 1,3-diene, that is, the dienophile can approach above or below the diene, we used the expressions "above" and "below" to distinguish the modes of addition. As shown in Scheme 6, isomers **1**, **7**, and **8** are more stable than their conformers (**1′**, **7′**, and **8′**) with the pyroglutamate group rotated by around 180°. In contrast, **6′** is more stable than **6** by 0.94 kcal mol^{-1}, and the expected **6**/**6′** ratio is 17:83. Therefore, **6′** is the major isomer, but **6** is energetically competitive for the cycloaddition process.

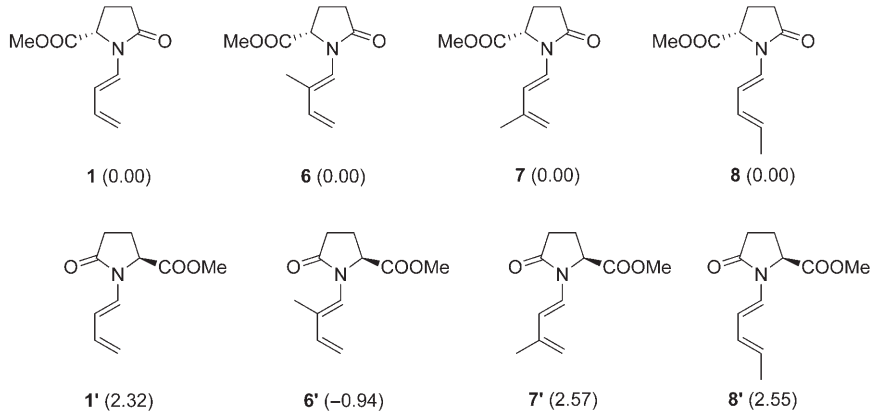
Scheme 7 shows the calculated final relative Gibbs free energies for the *endo* addition with the formation of the two diastereomeric products *endo*-**2a** and *endo*-**2b**; their transition states are TS-*endo*-**2**-above and TS-*endo*-**2**-below, respectively. Both the transition state TS-*endo*-**2**-above and the product *endo*-**2a** are clearly lower in Gibbs free energy than the corresponding TS-*endo*-**2**-below and *endo*-**2b** by 5.24 and 5.23 kcal mol^{-1}, respectively. This indicates that



Scheme 7. Calculated final relative Gibbs free energies (kcal mol^{-1}) of the possible products and transition states (TSs) for the *endo* cycloaddition of dienamide **1** to *N*-methyl maleimide.

endo-**2a** is favored both kinetically and thermodynamically. Given the large difference between TS-*endo*-**2**-above and TS-*endo*-**2**-below in Gibbs free energy (5.24 kcal mol^{-1}), *endo*-**2a** should be the only product.

As in case of the substituted oxazolidinone derivatives, the diastereoselectivity of dienamide **1** is also controlled by the energy difference of the transition states TS-*endo*-**2**-above and TS-*endo*-**2**-below. As shown in Figure 1, the energy difference has a steric rather than electronic origin. For example, in TS-*endo*-**2**-above, both the ester group and dienophile are on opposite sides of the 1,3-butadiene moiety; they are on the same side in TS-*endo*-**2**-below. Apart from the distances involved in C–C bond formation, the shortest nonbonding distance is also very interesting. In TS-*endo*-**2**-above, the shortest nonbonding distances between the oxygen atom of the dienophile and the hydrogen atom of the pyroglutamate ring are 2.613 and 2.755 Å. In TS-*endo*-**2**-below, the shortest nonbonding distance between the oxygen atom of the dienophile and the hydrogen atom of



Scheme 6. Calculated methyl-substituted *N*-dienyl pyroglutamates. Relative Gibbs free energies (kcal mol^{-1}) are given in parentheses.

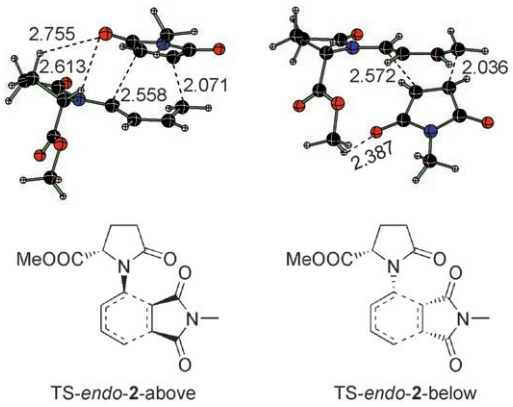


Figure 1. B3LYP/6–31G*-optimized transition states for the formation of *endo*-**2a** and *endo*-**2b**.

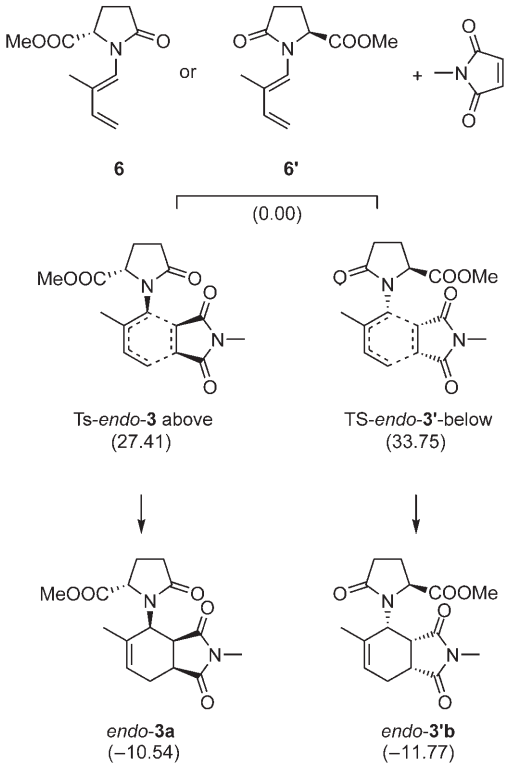
ester group is 2.387 Å. This reveals clearly the steric difference between the two transition states.

Next, we were interested in the influence of methyl substitution at the 1,3-dienyl moiety on diastereoselectivity (**6**–**8**, Scheme 6). The calculated Gibbs free energies for the respective transition states and products are shown in Scheme 8.

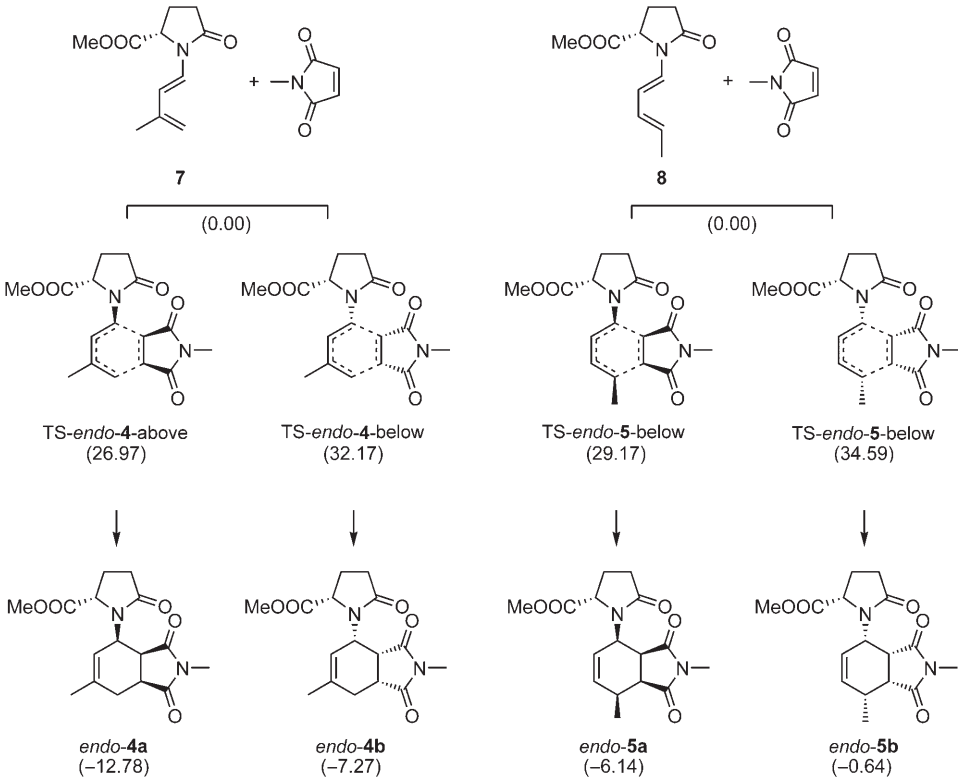
As dienamides **6** and **6′** are close in energy, we calculated the energies for the more-favored competitive reactions. As shown in Scheme 8, TS-*endo*-**3**-above is lower in Gibbs free energy than TS-*endo*-**3′**-below by 6.34 kcal mol^{-1}; therefore, *endo*-**3a** should be the only product despite the lower energy of **6′**.

As shown in Scheme 9, the products *endo*-**4a** and *endo*-**5a** are favored both kinetically and thermodynamically. The differences in Gibbs free energy of the transition states (5.20 and 5.42 kcal mol^{-1}, respectively) reveal the diastereoselectivity and confirm *endo*-**4a** and *endo*-**5a** as the principal products.

Compared to the experimentally determined diastereoselectivities (*de*), the theoretical computations predicted higher diastereoselectivities for the pyroglutamate derivatives (Table 1, 67–82% *de*); that is, in all cases, only one diastereomer is expected. Nevertheless, both theory and experiment showed the same trend in favor of diastereoselectivity, and the predicted major products are in agreement with the experimentally obtained results (see the conformational analysis discussed below).



Scheme 8. Calculated final relative Gibbs free energies (kcal mol^{-1}) of the possible products and transition states (TSs) for the *endo* cycloaddition of dienamides **6** and **6′** to *N*-methyl maleimide.



Scheme 9. Calculated final relative Gibbs free energies (kcal mol^{-1}) of the possible products and transition states (TSs) for the *endo* cycloaddition of dienamides **7** and **8** to *N*-methyl maleimide.

In the course of our detailed structural investigations, we observed some interesting features for the pyroglutamate derivatives. For the diastereomers **2a** and **3**, suitable crystals were obtained for X-ray diffraction analysis (Figure 2), which confirmed the *endo* configuration at the cyclohexene ring.

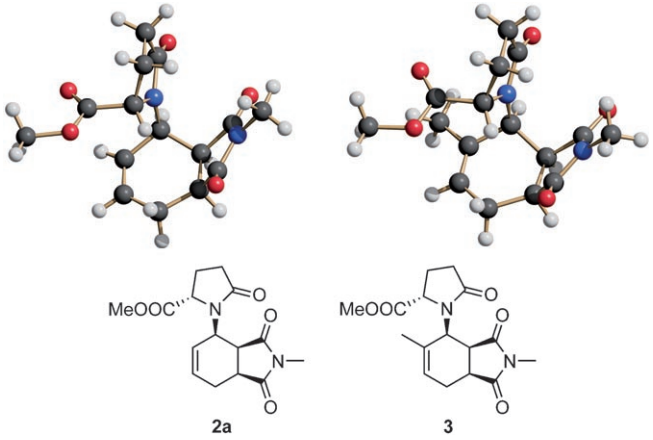
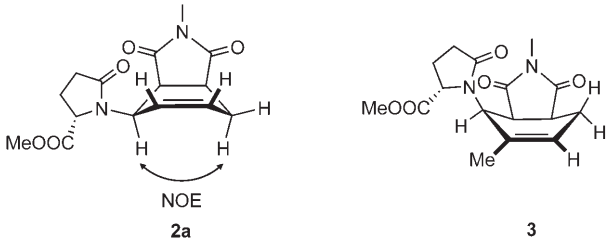


Figure 2. X-ray diffraction analysis of the pyroglutamate derivatives (*S*)-methyl-1-((3a*S*,4*R*,7a*S*)-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-5-oxopyrrolidine-2-carboxylate (**2a**) and (*S*)-methyl-1-((3a*S*,4*S*,7a*S*)-2,5-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-5-oxopyrrolidine-2-carboxylate (**3**).

Although the X-ray data do not allow any conclusions regarding the absolute configurations, the relative configurations of the different substituents can be deduced. Hence, provided that the pyroglutamate moiety does not racemize during the course of the reaction, the structures of the diastereomers **2a** and **3** can be determined as presented in Figure 2. Interestingly, for both AAD products a boat-shaped cyclohexene ring was found in the solid state, in which the amide moiety settles in an axial position. On the basis of NOE measurements in solution, **2a** was found to have a boat-shaped conformation with the pyroglutamate moiety in an equatorial position, which implies conformational changes between the solid and solution states. In contrast, NOE experiments on **3** showed no correlation for 4-H and 7-H, thus indicating that **3** exhibits the same conformation in both solid state and solution. This is most likely due to the *ortho*-substituted methyl group (Scheme 10). The possibility of the cyclohexene ring in such bicyclic structures to exist in two different conformations (boat-shaped concave and boat-shaped convex) has also been confirmed in similar compounds of this type.[23]



Scheme 10. Conformation of the pyroglutamate derivatives **2a** and **3** as found in solution (**2a**: boat-shaped concave conformation of cyclohexene ring; **3**: boat-shaped convex conformation of cyclohexene ring).

The different features observed for **2a** and **3** led us to a detailed analysis of the possible conformations of the AAD derivatives and their energy differences. Along with the boat-shaped conformation, we also took the X-ray structures of **2a** and **3** for direct comparison. As there are no X-ray structures for **4a** and **5a** available, we modified their structures on the basis of the X-ray structures of **2a** and **3**. The calculated results are shown in Figure 3, in which only the skeletal structures of the annulated five- and six-membered rings are displayed to give a concise overview. The first structure has a boat-shaped cyclohexene ring with the pyroglutamate moiety in an equatorial position (N-eq). The second one exhibits a twisted boat-shaped cyclohexene ring with the pyroglutamate in an axial position (N-axial).

For **2a**, the N-axial arrangement is the less-stable conformation (by 4.15 kcal mol^{-1}). This is in agreement with the results of NMR spectroscopy stated above. The NOE interactions between 4-H and 7-H were also observed for **4a** and **5a**, in which the methyl substituent is positioned *meta* and *para* to the amide residue, respectively. These experimental

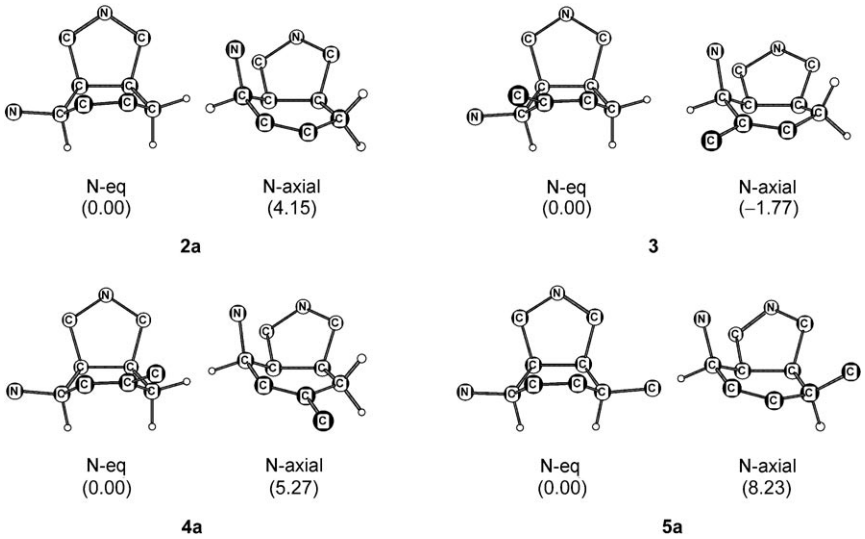


Figure 3. Possible conformers of the boat-shaped cyclohexene ring in the pyroglutamate derivatives **2a**, **3**, **4a**, and **5a** with the pyroglutamate moiety in the axial (N-axial) and equatorial (N-eq) positions. The corresponding relative free Gibbs energies are also given (kcal mol^{-1}).

results perfectly fit the calculations. For **4a** and **5a**, the N-eq conformers are more stable; the N-axial conformers are higher in energy. It is unfortunate that X-ray structure analysis is not available for these two compounds, therefore it is hard to speculate on their structures in the solid state.

However, NMR spectroscopic and X-ray analysis of the *ortho*-methylated derivative **3** allude to a boat-shaped cyclohexene ring with the amide moiety in an axial position (Scheme 10) in both the solid state and in solution. This is also in agreement with the calculations. As shown in Figure 3, the N-axial conformation is more stable than the N-eq, which is most likely due to the ecliptic arrangement of the methyl group and the amide moiety in N-eq.

Interestingly, we succeeded in preparing the bromo-substituted AAD derivative **9** (Figure 4) simply by utilizing α-bromocrotonaldehyde, (*S*)-methyl pyroglutamate, and *N*-methyl

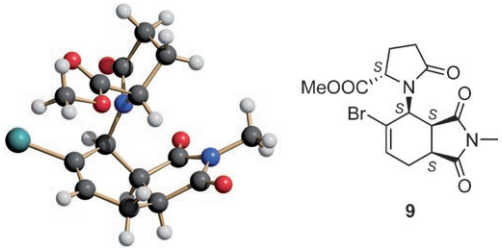


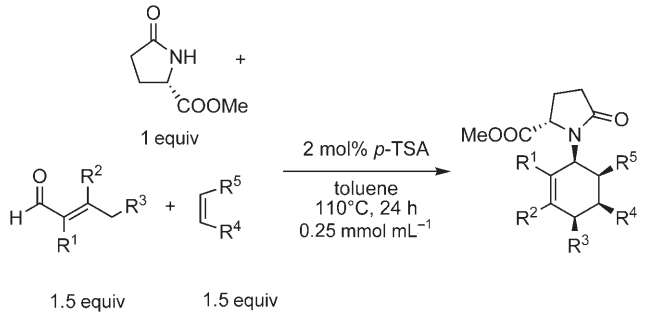
Figure 4. X-ray diffraction analysis of the bromo-substituted pyroglutamate derivative (*S*)-methyl-1-((3a*S*,4*S*,7a*S*)-5-bromo-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-5-oxopyrrolidine-2-carboxylate (**9**).

maleimide. Owing to the heavy atom, the crystallographic structure confirmed the absolute configuration of all stereocenters to be (*S*,*S*,*S*,*S*). Hence, racemization clearly does not occur at the pyroglutamatic stereocenter throughout the reaction, which also confirms the structures of **2a** and **3** shown. In a NOESY spectrum recorded for **9**, no correlation between the protons 4-H and 7-H was found. Therefore, it can be concluded that the same conformation (boat-shaped convex) with the amide moiety in an axial position exists in solution and in the solid state, in analogy with compound **3** (Scheme 10).

Next, we set out to extend the diastereoselective AAD protocol to different aldehydes and dienophiles. Table 2 summarizes the results obtained. In general, the corresponding products were isolated in good yields (Table 2, entries 1 and 3–6, 55–82%). The diastereoselective AAD reaction tolerates various aldehydes (linear, branched, with aromatic as well as aliphatic substituents).

In the case of citral as the aldehyde component, the two AAD products **11** and **12** (Table 2, entry 2), corresponding to the *E* and *Z* aldehyde, respectively, were obtained in an overall yield of 70%. When compound **14** was prepared (Table 2, entry 4) the butterfly-like diazatetradecene **18** (Scheme 11) was isolated as a by-product in 14% yield. This type of compound is well-known in our group and is gener-

Table 2. Scope of the diastereoselective AAD protocol with (*S*)-methyl pyroglutamate as the amide component.



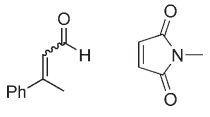
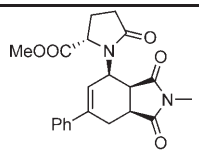
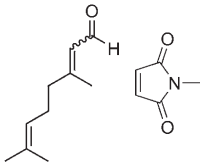
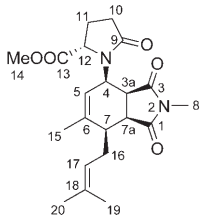
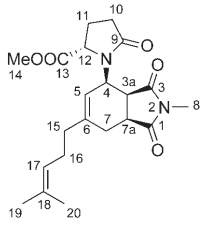
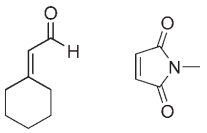
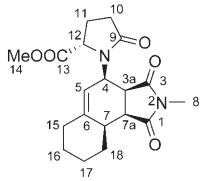
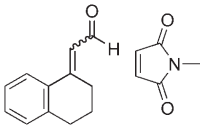
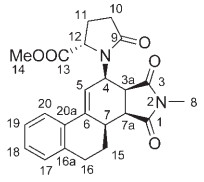
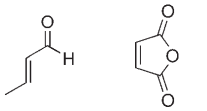
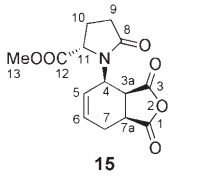
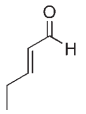
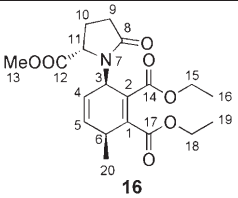
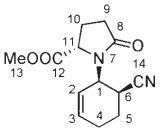
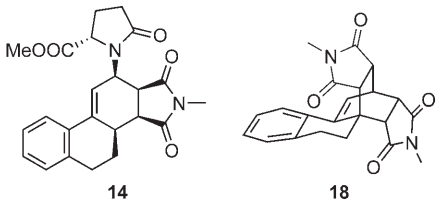
Entry	Aldehyde	Dienophile	AAD product	Yield [%][a]
1			 **10**	72
2			 **11**  **12**	38 32
3			 **13**	76
4			 **14**	55
5			 **15**	82[b]

Table 2. (Continued)

Entry	Aldehyde	Dienophile	AAD product	Yield [%][a]
6			 **16**	65[c]
7			 **17**	35[d]

[a] Yield of isolated product. [b] Addition of Ac_2O (1.5 equiv). [c] Addition of acetylenedicarboxylate (5 equiv); two *endo* isomers were isolated (80% *de*). [d] Addition of acrylonitrile (3 equiv), reaction for 3 days at 140 °C.



14 **18**

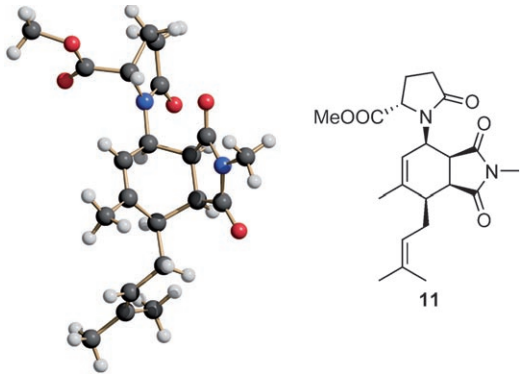
Scheme 11. By-product of compound **14**: the butterfly-like diazatetradecene **18**.

ally accessed by conversion of trifluoroacetic anhydride, α,β-unsaturated aldehydes, and dienophiles.[13]

Different dienophiles can also be employed in the one-pot procedure. Application of maleic anhydride (Table 2, entry 5) afforded the corresponding product in 82% yield. Here, Ac_2O was required as a water-removing agent to keep the anhydride ring closed. Acyclic dienophiles such as acetylenedicarboxylate can also be utilized successfully (Table 2, entry 6; 65%), although an excess of dienophile is required. In this case, the two *endo* isomers were isolated in a 90:10 ratio. Reaction with acrylonitrile as an unsymmetrical dienophile afforded the *ortho* adduct featuring adjacent amino and cyano substituents (Table 2, entry 7). Owing to the lower reactivity of this dienophile, an excess of the reagent and longer reaction times were again required.

Apart from compounds **16a** and **16b** (Table 2, entry 6), the expected main diastereomers for the AAD products **9**–**15** and **17** were isolated in high purity and could, therefore, be characterized. Given the experience gained with the pyroglutamic derivatives **2**, **4**, and **5**, the formation of minor stereoisomers is, in principle, assumed.

X-ray diffraction analysis was possible for compound **11** (Table 2, entry 2). The structure is depicted in Figure 5. The X-ray data confirm the relative all-*syn* configuration of the substituents at the cylohexene ring as well as their relative



11

Figure 5. X-ray diffraction analysis of the pyroglutamate derivative (*S*)-methyl-1-((3a*S*,4*R*,7*R*,7a*S*)-2,6-dimethyl-7-(3-methylbut-2-enyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-5-oxopyrrolidine-2-carboxylate (**11**).

configuration to the stereocenter of the pyroglutamate moiety.

The stereochemistry of the compounds given in Tables 1 (**2**, **3**, **4a**, and **5a**) and 2 (**10**–**14**) is confirmed in solution by NMR spectroscopy. As stated in our previous publication,[14] a decision between **a** (major) and **b** (minor) diastereomers can be taken on the basis of chemical shifts, coupling constants, and the results of NOE measurements. For example, for the **a** diastereomers, the chemical shifts for 3a-H ($\delta =$ 3.50–3.80 ppm) were significantly shifted downfield relative to those of the **b** diastereomers ($\delta = 3.20$–3.35 ppm). Furthermore, the coupling constants between 3a-H and 4-H ($^3J_{3a\text{-}H,4\text{-}H} = 6.5$–$7.5$ Hz) for the **a** diastereomers are characteristically lower than those of the **b** diastereomers by about 2 Hz ($^3J_{3a\text{-}H,4\text{-}H} = 8.8$–$9.2$ Hz). These values can be expected if both diastereomers have a boat-shaped concave conformation of the cyclohexene ring with a bis-axial arrangement of protons 4-H and 7-H, which can be proved by NOE measurements. For example, NOE correlations were found in the NOESY spectra of **2**, **4a**, **5a**, **11**, **13**, and **14**, thus confirming that the protons 4-H and 7-H are bis-axially arranged, and that the amide moiety has an equatorial position in solution. It can be concluded, even if no NOESY spectrum was measured, that the configuration can be assigned if the chemical shift of 3a-H and the coupling constant $^3J_{3a\text{-}H,4\text{-}H}$ is found to be in the range given above, which is the case for compounds **10** and **12**. On the basis of all these NMR spectroscopic results, compounds **10**–**15** appear as **a** diastereomers. As already mentioned, no correlations were found for the protons 4-H and 7-H in the NOESY spectra of **3** and **9**, thus indicating another conformation (boat-shaped convex) of the cyclohexene ring, which is shown for **3** in Scheme 10. For compounds **16a** and **16b**, the relative *syn* configuration of the substituents at the cylohexene ring was confirmed as proved by NOE correlations between 3-H and 6-H. However, their relative configuration to the ester group of the pyroglutamate moiety could not be determined.

Conclusions

(*S*)-Methyl pyroglutamate is a convenient chiral amide component for diastereoselective AAD reactions even when sterically more-demanding substituents are present. A number of diversely substituted asymmetric pyroglutamate derivatives has been prepared in up to 82% yield. DFT calculations revealed that the diastereoselectivity is due to both kinetic and thermodynamic control. X-ray diffraction and comprehensive NMR spectroscopic analysis allowed detailed structural investigations in solution and the solid state.

Experimental Section

Computational Details

Owing to the large number of substituted 1,4-butadienes and the corresponding transition states as well as addition products, the computational work was done in several steps. All these data are summarized in the Supporting Information. All calculations were carried out by using the Gaussian 03 program package.[24] Geometry optimizations were done firstly at the HF/6–31G* level, then refined at the B3LYP/6–31G* level. For the more (or most) energetically favored transition states and their products, both HF/6–31G* and B3LYP/6–31G* frequency calculations were carried out to characterize the optimized structures as energy-minimum structures without imaginary frequencies ($N_{Imag}=0$), only real frequencies, and the transition states have only one imaginary frequency ($N_{Imag}=1$).[25] For the less energetically favored (or unfavored) transition states and their products, only HF/6–31G* frequency calculations were done. There are qualitative differences between the B3LYP/6–31G* and HF/6–31G* frequency calculations. Single-point energy calculations were carried out at the B3LYP/6–311+G* level on the B3LYP/6–31G* optimized geometries. The thermal-energy corrections at B3LYP/6–31G* from the frequency calculations were added to the final Gibbs free energies to analyze the selectivity. The final Gibbs energies are the sum of the relative energies from the B3LYP/6–311+G*//B3LYP/6–31G* single-point energy calculations and the thermal corrections at B3LYP/6–31G* scaled at 298 K. As the experimental reactions were carried out over the temperature range 100–160 °C, the selectivity was estimated at approximately 400 K based on the relationship $\Delta\Delta G^{\neq}=-RT\ln K$, in which $\Delta\Delta G^{\neq}$ is the difference in the Gibbs free activation energy, and K is the considered equilibrium constant of the two competing transition states.

General Experimental Details

Typically, AAD reactions were run in ACE pressure tubes and Wheaton reaction vials from Aldrich. Unless otherwise noted, all reagents were used as received from commercial suppliers. Silica-gel column chromatography was performed with silica gel 60 (particle size 0.063–0.2 mm) from Fluka or Acros. Melting points were recorded on a Leica Galen III apparatus (Cambridge Instruments) and are uncorrected. IR spectra of solids were recorded as nujol mulls with KBr plates or pellets on a Nicolet Magna 550 spectrometer; liquids were analyzed neat. Mass spectra were obtained on an AMD 402/3 spectrometer from AMD Intectra (EI, 70 eV). NMR spectra were recorded on Bruker AV 500 (^{1}H 500.13 MHz, ^{13}C 125.8 MHz), AV 400 (^{1}H 400.13 MHz, ^{13}C 100.6 MHz), and AV 300 spectrometers (^{1}H 300.13 MHz, ^{13}C 75.0 MHz). Calibration of spectra was carried out with the solvent signals ($CDCl_3$: $\delta(^1H)=7.25$, $\delta(^{13}C)=77.0$ ppm). The NMR signals were assigned by DEPT and two-dimensional ^{1}H,^{1}H COSY and ^{1}H,^{13}C correlation spectra (HSQC, HMBC, and HETCOR). For the determination of the stereochemistry of **2**, **3**, **4a**, **5a**, **9**, **11**, **13**, and **14**, ^{1}H,^{1}H NOESY spectra were recorded. Crystallographic data of **2a**, **3**, **9**, and **11** were collected on a STOE-IPDS diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation. The structures were solved by direct methods (SHELXS-97)[26] and refined by full-matrix least-squares against F^2 (SHELXL-97).[27] Schakal was used for structural representations.

Crystal data for **2a**: space group $P2_12_12_1$, orthorhombic, $a=6.722(1)$, $b=10.249(2)$, $c=21.492(4)$ Å, $\beta=90°$, $V=1480.7(5)$ Å^3, $Z=4$, $\rho_{calcd}=1.374$ g cm^{-3}, 24505 reflections measured, 3407 independent of symmetry, of which 3117 observed ($I>2\sigma(I)$), $R1=0.0264$, $wR2$ (all data)$=0.0692$, 200 parameters. Crystal data for **3**: space group $P2_12_12_1$, orthorhombic, $a=6.883(1)$, $b=10.443(2)$, $c=21.537(4)$ Å, $\beta=90°$, $V=1548.1(5)$ Å^3, $Z=4$, $\rho_{calcd}=1.374$ g cm^{-3}, 10071 reflections measured, 2998 independent of symmetry, of which 2245 observed ($I>2\sigma(I)$), $R1=0.0427$, $wR2$ (all data)$=0.1015$, 208 parameters. Crystal data for **9**: space group $P2_12_12_1$, orthorhombic, $a=6.847(1)$, $b=10.379(2)$, $c=21.860(4)$ Å, $\beta=90°$, $V=1553.5(5)$ Å^3, $Z=4$, $\rho_{calcd}=1.647$ g cm^{-3}, 12168 reflections measured, 2933 independent of symmetry, of which 2568 observed ($I>2\sigma(I)$), $R1=0.0297$, $wR2$ (all data)$=0.0722$, 208 parameters. Crystal data for **11**: space group $P2_1$, monoclinic, $a=13.900(3)$, $b=8.942(2)$, $c=16.497(3)$ Å, $\beta=102.71(3)°$, $V=2000.2(7)$ Å^3, $Z=4$, $\rho_{calcd}=1.290$ g cm^{-3}, 13001 reflections measured, 7630 independent of symmetry, of which 4473 observed ($I>2\sigma(I)$), $R1=0.0450$, $wR2$ (all data)$=0.0904$, 505 parameters.

CCDC-634301 (**2a**), -634303 (**3**), -634304 (**9**), and -634302 (**11**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for the Preparation of 2–5 and 10–18

The chiral amide (1 equiv) was placed in a threaded pressure tube, then toluene (0.25 mmol mL^{-1}), aldehyde (1.5 equiv), dienophile (1.5 equiv), and *p*-toluenesulfonic acid monohydrate (2 mol%) were added. The reaction mixture was stirred at elevated temperatures (110–160 °C) for 24 h (for acrylonitrile: 3 days). After cooling, all volatile compounds were removed under reduced pressure. For detailed conditions (temperature, time) and workup procedures (silica-gel chromatography or precipitation), see the paragraph pertinent to the respective product. The corresponding α,β-unsaturated aldehydes for **10**, **13**, and **14** were prepared according to the literature procedure.[28]

Sample Preparation for Determination of Diastereoselectivity

The chiral amide (0.5 mmol) was placed in a 5-mL Wheaton reaction vial, then toluene (2 mL), aldehyde (0.75 mmol), dienophile (0.75 mmol), and *p*-toluenesulfonic acid monohydrate (2 mol%) were added. The reaction mixture was stirred at 110 °C for 24 h. After cooling, all volatile compounds were removed under reduced pressure. The residue was dissolved in $CDCl_3$ (1 mL) and subjected to ^{13}C NMR (IG) analysis.

For **2–5** as well as **9** and **10**, the assignment of the NMR signals was carried out according to the numbering given in Table 1. For **11–17**, the numbering is given in Table 2. The numbering may not always correspond to the names of the compounds, but was chosen for consistent assignment of the NMR data.

Analytical Data

2: Methyl 1-(2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-5-oxopyrrolidine-2-carboxylate, conditions: 110 °C, 24 h, silica-gel chromatography, 77% yield, 74% *de* (^{13}C IG NMR). **2a**: $R_f=0.17$ (SiO_2, *n*-heptane/EtOAc=1:5); m.p.: 110–111 °C; IR (KBr): $\tilde{\nu}=3437$ (m), 3008 (w), 2958 (m), 2876 (w), 1751 (vs), 1690 (vs), 1435 (s), 1416 (s), 1381 (m), 1337 (m), 1322 (w), 1283 (s), 1248 (m), 1240 (m), 1206 (s), 1178 (m), 1126 (m), 1095 (w), 1079 (w), 1063 (w), 1046 (m), 1019 (m), 1003 (m), 983 (m), 971 (w), 956 (w), 937 (w), 892 (m), 813 (w), 801 (m), 767 (m), 723 (w), 705 (m), 675 (m), 632 (m), 580 (m), 555 (m), 502 (m), 421 cm^{-1} (w); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=2.08$ (m; 1H of CH_2), 2.16 (qq*, $^2J_{7\text{-Hax},7\text{-Heq}}=15.8$ Hz, $^3J_{7\text{-Hax},7a\text{-H}}=8.0$ Hz, $^4J_{7\text{-Hax},5\text{-H}}=3.3$ Hz, $^3J_{7\text{-Hax},6\text{-H}}=3.0$ Hz, 1H; 7-H$_{ax}$), 2.36–2.45 (m; 1H of CH_2), 2.53–2.66 (m, 2H; CH_2), 2.75 (ddd, $^2J_{7\text{-Heq},7\text{-Hax}}=15.8$ Hz, $^3J_{7\text{-Heq},6\text{-H}}=7.2$ Hz, $^3J_{7\text{-Heq},7a\text{-H}}=1.6$ Hz, 1H; 7-H$_{eq}$), 2.88 (s, 3H; 8-H), 3.15 (ddd, $^3J_{7a\text{-H},3a\text{-H}}=9.0$ Hz, $^3J_{7a\text{-H},7\text{-Hax}}=8.0$ Hz, $^3J_{7a\text{-H},7\text{-Heq}}=1.6$ Hz, 1H; 7a-H), 3.63 (dd, $^3J_{3a\text{-H},7a\text{-H}}=9.0$ Hz, $^3J_{3a\text{-H},4\text{-H}}=6.6$ Hz, 1H; 3a-H), 3.75 (s, 3H; 14-H), 4.36 (m, 1H; 12-H), 4.75 (m, 1H; 4-H), 5.68 (dt*, $^3J_{5\text{-H},6\text{-H}}=9.8$ Hz, $^4J_{5\text{-H},7\text{-Hax}}=3.3$ Hz, $^3J_{5\text{-H},4\text{-H}}=3.0$ Hz, 1H; 5-H), 5.92 ppm (m, 1H; 6-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=24.1$

(C7), 24.9 (C8), 25.0 (CH_2), 29.7 (CH_2), 38.3 (C7a), 41.8 (C3a), 48.8 (C4), 52.7 (C14), 59.7 (C12), 126.1 (C5), 129.1 (C6), 173.8 (CO), 175.9 (CO), 177.5 (CO), 179.3 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 306 (17) $[M]^+$, 247 (47) $[M-C_2H_3O_2]^+$, 219 (16), 195 (20), 164 (14), 142 (51), 136 (57), 108 (10), 84 (100), 79 (58), 77 (27), 53 (11), 41 (16), 28 (15), no further peaks >10%; HRMS (EI, 70 eV): *m/z* calcd for $C_{15}H_{18}N_2O_5$: 306.1216 $[M]^+$; found: 306.1208. **2b**: R_f = 0.09 (SiO_2, *n*-heptane/EtOAc = 1:5); NMR data were extracted from a spectrum of a mixture of **2a** and **2b**; not all signals are given due to overlap with signals of the major diastereomer **2a**; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.88 (s, 3H; 8-H), 3.07 (dt*, $^3J_{7a\text{-}H,3a\text{-}H}$ = 8.5 Hz, $^3J_{7a\text{-}H,7\text{-}Hax}$ = 3.2 Hz, $^3J_{7a\text{-}H,7\text{-}Heq}$ = 3.2 Hz, 1H; 7a-H), 3.27 (t*, $^3J_{3a\text{-}H,4\text{-}H}$ = 8.8 Hz, $^3J_{3a\text{-}H,7a\text{-}H}$ = 8.5 Hz, 1H; 3a-H), 3.75 (s, 3H; 14-H), 4.15 (m, 1H; 4-H), 4.49 (m, 1H; 12-H), 5.92 (m, 1H; 6-H), 6.03 ppm (dt*, $^3J_{5\text{-}H,6\text{-}H}$ = 9.9 Hz, $^4J_{5\text{-}H,7\text{-}Hax}$ = 3.2 Hz, $^3J_{5\text{-}H,4\text{-}H}$ = 3.2 Hz, 1H; 5-H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 22.2 (CH_2), 23.7 (CH_2), 24.9 (C8), 30.0 (CH_2), 39.0 (C7a), 41.6 (C3a), 49.4 (C4), 52.5 (C14), 61.3 (C12), 126.7 (C6), 127.4 (C5), 172.9 (CO), 175.9 (CO), 177.1 (CO), 179.0 ppm (CO).

3: Methyl 1-(2,5-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-5-oxopyrrolidine-2-carboxylate, conditions: 160°C, 24 h, precipitation, 48% yield. R_f = 0.13 (SiO_2, *n*-heptane/EtOAc = 1:5); m.p.: 221–224°C; IR (nujol): $\tilde{\nu}$ = 3447 (w), 3358 (w), 2724 (w), 1743 (vs), 1699 (vs), 1345 (m), 1309 (m), 1300 (w), 1277 (m), 1237 (m), 1210 (m), 1173 (m), 1150 (m), 1134 (m), 1061 (w), 1039(m), 1026 (w), 1015 (w), 981 (w), 958 (m), 907 (m), 885 (w), 838 (m), 808 (m), 797 (m), 771 (m), 760 (m), 730 (m), 701 (m), 657 (m), 634 (m), 610 (m), 577 (m), 551 (m), 512 (m), 450 (m), 441 cm^{-1} (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.67 (br, 3H; CH_3C), 1.87–2.00 (m, 2H; 11-H), 2.29–2.35 (m; 1H of 10-H), 2.32–2.39 (m, 1H; 7-H_{ax}), 2.45–2.56 (m; 1H of 10-H), 2.63 (dddq, $^2J_{7\text{-}Heq,7\text{-}Hax}$ = 18.0 Hz, $^3J_{7\text{-}Heq,7a\text{-}H}$ = 10.2 Hz, $^3J_{7\text{-}Heq,6\text{-}H}$ = 6.6 Hz, $^5J_{7\text{-}Heq,CH3}$ = 1.2 Hz, 1H; 7-H_{eq}), 2.96 (s, 3H; 8-H), 3.11 (dt*, $^3J_{7a\text{-}H,3a\text{-}H}$ = 10.2 Hz, $^3J_{7a\text{-}H,7\text{-}Heq}$ = 10.2 Hz, $^3J_{7a\text{-}H,7\text{-}Hax}$ = 8.0 Hz, 1H; 7a-H), 3.31 (dd, $^3J_{3a\text{-}H,7a\text{-}H}$ = 10.2 Hz, $^3J_{3a\text{-}H,4\text{-}H}$ = 8.5 Hz, 1H; 3a-H), 3.62 (s, 3H; 14-H), 3.48 (dd, $^3J_{11\text{-}H,12\text{-}H}$ = 8.5, 1.5 Hz, 1H; 12-H), 5.22 (d, $^3J_{4\text{-}H,3a\text{-}H}$ = 8.5 Hz, 1H; 4-H), 5.68 ppm (m, 1H; 6-H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 21.9 (*C*H_3C), 22.4 (C7), 24.1 (C11), 24.7 (C8), 28.3 (C10), 37.2 (C7a), 42.0 (C3a), 47.2 (C4), 52.0 (C14), 58.4 (C12), 125.4 (C6), 131.9 (C5), 172.0 (CO), 175.6 (CO), 176.2 (CO), 179.4 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 320 (32) $[M]^+$, 261 (12) $[M-C_2H_3O_2]^+$, 233 (11), 204 (11), 193 (12), 177 (38), 150 (15), 144 (32), 142 (18), 93 (51), 84 (100), 77 (21), 41 (16), 28 (17), no further peaks >10%; HRMS (EI, 70 eV): *m/z* calcd for $C_{16}H_{20}N_2O_5$: 320.1372 $[M]^+$; found: 320.1377.

4: Methyl 1-(2,6-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-5-oxopyrrolidine-2-carboxylate, conditions: 110°C, 24 h, silica-gel chromatography, 82% yield, 67% *de* (^{13}C IG NMR). **4a**: R_f = 0.24 (SiO_2, *n*-heptane/EtOAc = 1:5); IR (nujol): $\tilde{\nu}$ = 3456 (m), 1747 (s), 1343 (s), 1294 (s), 1111 (m), 1079 (m), 1048 (m), 1028 (m), 999 (m), 947 (w), 913 (w), 891 (w), 845 (w), 805 (m), 769 (m), 736 (w), 679 (m), 626 (m), 580 (m), 545 (w), 514 (w), 467 cm^{-1} (w); MS (EI, 70 eV): *m/z* (%) = 320 (57) $[M]^+$, 292 (17), 277 (22), 264 (31), 261 (20) $[M-C_2H_3O_2]^+$, 233 (24), 209 (18), 204 (30), 178 (31), 177 (19), 150 (62), 144 (11), 142 (11), 93 (71), 84 (100), 77 (34), 67 (15), 43 (57), 28 (61), no further peaks >10%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65 (s, 3H; CH_3), 1.98–2.03 (m; 1H of 10-H), 2.11–2.19 (m, 1H; 7-H_{ax}), 2.32–2.38 (m; 1H of 11-H), 2.47–2.57 (m, 3H; 1H each of 7-H_{eq}, 10-H, 11-H), 2.82 (s, 3H; 8-H), 3.06 (ddd, $^3J_{7a\text{-}H,3a\text{-}H}$ = 9.0 Hz, $^3J_{7a\text{-}H,7\text{-}Hax}$ = 7.5 Hz, $^3J_{7a\text{-}H,7\text{-}Heq}$ = 1.8 Hz, 1H; 7a-H), 3.50 (dd, $^3J_{3a\text{-}H,7a\text{-}H}$ = 9.0 Hz, $^3J_{3a\text{-}H,4\text{-}H}$ = 6.9 Hz, 1H; 3a-H), 3.69 (s, 3H; 14-H), 4.22 (m, 1H; 12-H), 4.67–4.71 (br m, 1H; 4-H), 5.22 ppm (br s, 1H; 5-H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 23.3 (CH_3), 24.63 (C10), 24.59 (C8), 28.6 (CH_2), 29.3 (CH_2), 38.2 (C7a), 41.2 (C3a), 48.8 (C4), 52.4 (C14), 59.3 (C12), 117.8 (C5), 138.3 (C6), 173.5 (CO), 175.9 (CO), 177.2 (CO), 178.9 ppm (CO); HRMS (EI, 70 eV): *m/z* calcd for $C_{16}H_{20}N_2O_5$: 320.1372 $[M]^+$; found: 320.1369. **4b**: NMR data were extracted from a spectrum of the crude reaction mixture of **4**; not all signals are given due to overlap with signals of the major diastereomer **4a**; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.66 (s, 3H; 14-H), 5.39 ppm (br s, 1H; 5-H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 23.2 (CH_3), 28.7 (CH_2), 29.5 (CH_2), 38.3 (C7a), 41.1 (C3a), 49.0 (C4), 52.0 (C14), 59.4 (C12), 118.2 (C5), 174.8 (CO), 176.1 (CO), 177.3 (CO), 179.0 ppm (CO).

5: Methyl 1-(2,7-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-5-oxopyrrolidine-2-carboxylate, conditions: 110°C, 24 h, silica-gel chromatography, 78% yield, 82% *de* (^{13}C IG NMR). **5a**: R_f = 0.24 (SiO_2, *n*-heptane/EtOAc = 1:5); m.p.: 120–122°C; IR (KBr): $\tilde{\nu}$ = 3434 (m), 2983 (w), 2954 (m), 2881 (w), 1752 (s), 1686 (vs), 1436 (s), 1417 (s), 1381 (m), 1336 (m), 1317 (w), 1283 (s), 1253 (m), 1202 (s), 1179 (m), 1107 (m), 1067 (w), 1052 (w), 1033 (w), 1012 (w), 986 (w), 964 (w), 953 (w), 896 (w), 877 (w), 815 (w), 800 (m), 783 (w), 738 (w), 701 (m), 689 (m), 629 (w), 580 (w), 563 (w), 531 (w), 478 (w), 425 cm^{-1} (w); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (d, $^3J_{7\text{-}H,CH3}$ = 7.5 Hz, 3H; CH_3), 2.04–2.13 (m; 1H of 10-H), 2.38–2.43 (m; 1H of 11-H), 2.43–2.49 (m, 1H; 7-H), 2.52–2.66 (m, 2H; 1H each of 10-H, 11-H), 2.85 (s, 3H; 8-H), 3.03 (dd, $^3J_{7a\text{-}H,3a\text{-}H}$ = 8.5 Hz, $^3J_{7a\text{-}H,7\text{-}H}$ = 7.3 Hz, 1H; 7a-H), 3.63 (dd, $^3J_{3a\text{-}H,7a\text{-}H}$ = 8.5 Hz, $^3J_{3a\text{-}H,4\text{-}H}$ = 6.5 Hz, 1H; 3a-H), 3.75 (s, 3H; 14-H), 4.43 (m, 1H; 12-H), 4.69 (m, 1H; 4-H), 5.65 (dt*, $^3J_{5\text{-}H,6\text{-}H}$ = 9.5 Hz, $^3J_{5\text{-}H,4\text{-}H}$ = 3.2 Hz, $^4J_{5\text{-}H,7\text{-}H}$ = 3.2 Hz, 1H; 5-H), 5.71 ppm (dt*, $^3J_{6\text{-}H,5\text{-}H}$ = 9.5 Hz, $^3J_{6\text{-}H,7\text{-}H}$ = 3.2 Hz, $^4J_{6\text{-}H,4\text{-}H}$ = 3.2 Hz, 1H; 6-H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 16.6 (CH_3), 24.6 (C8), 24.9 (C10), 29.6 (C11), 30.8 (C7), 42.9 (C3a), 43.2 (C7a), 49.3 (C4), 52.6 (C14), 59.8 (C12), 124.9 (C5), 135.5 (C6), 173.8 (CO), 175.9 (CO), 176.8 (CO), 177.3 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 320 (26) $[M]^+$, 261 (39) $[M-C_2H_3O_2]^+$, 233 (21), 209 (97), 178 (14), 150 (88), 142 (39), 122 (12), 93 (46), 84 (100), 77 (22), 67 (13), 41 (16), 28 (10), no further peaks >10%; HRMS (EI, 70 eV): *m/z* calcd for $C_{16}H_{20}N_2O_5$: 320.1372 $[M]^+$; found: 320.1381. **5b**: NMR data were extracted from a spectrum of the crude reaction mixture of **5**; not all signals are given due to overlap with signals of the major diastereomer **5a**; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.45 (d, $^3J_{7\text{-}H,CH3}$ = 7.5 Hz, 3H; CH_3), 2.87 (s, 3H; 8-H), 3.74 (s, 3H; 14-H), 4.40 ppm (m, 1H; 12-H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 16.4 (CH_3), 30.5 (C7), 42.6 (C3a), 43.1 (C7a), 49.2 (C4), 52.4 (C14), 59.1 (C12), 123.4 (C5), 135.4 (C6), 173.5 (CO), 175.8 (CO), 176.5 ppm (CO).

9: (*S*)-Methyl pyroglutamate (1.00 mmol, 143 mg) was placed in a CEM pressure tube (10 mL), then toluene (2 mL), α-bromocrotonaldehyde (2.00 mmol, 298 mg), *N*-methyl maleimide (1.50 mmol, 167 mg), and *p*-toluenesulfonic acid monohydrate (2 mol%, 4 mg) were added. The reaction vessel was sealed, and the mixture was subject to microwave irradiation (max. 50 W, 2450 MHz) with stirring at 180°C for 40 min. After cooling, all volatile compounds were removed under reduced pressure. The product methyl 1-(5-bromo-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-5-oxopyrrolidin-2-carboxylate (**9**) was obtained by precipitation from ethyl acetate (46% yield). Further purification was not necessary. R_f = 0.22 (SiO_2, *n*-heptane/EtOAc = 1:5); m.p.: 228–229°C; IR (nujol): $\tilde{\nu}$ = 3449 (w), 3364 (w), 3046 (w), 3008 (w), 2977 (w), 1750 (s), 1702 (vs), 1439 (vs), 1397 (s), 1344 (m), 1321 (m), 1301 (m), 1280 (m), 1238 (m), 1209 (m), 1183 (m), 1152 (m), 1135 (m), 1071 (m), 1040 (w), 1028 (w), 988 (w), 957 (s), 937 (m), 908 (m), 858 (w), 827 (m), 817 (m), 798 (m), 770 (m), 758 (m), 707 (m), 686 (w), 668 (m), 656 (m), 633 (m), 614 (w), 593 (m), 573 (w), 552 (m), 527 (w), 501 (m), 438 cm^{-1} (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17–2.32 (m; 3H of CH_2), 2.51–2.59 (m; 1H of CH_2), 2.61 (dddd, $^2J_{7\text{-}Hax,7\text{-}Heq}$ = 17.6 Hz, $^3J_{7\text{-}Hax,7a\text{-}H}$ = 9.8 Hz, $^3J_{7\text{-}Hax,6\text{-}H}$ = 6.4 Hz, $^5J_{7\text{-}Hax,4\text{-}H}$ = 1.0 Hz, 1H; 7-H_{ax}), 2.75 (dddd, $^2J_{7\text{-}Heq,7\text{-}Hax}$ = 17.6 Hz, $^3J_{7\text{-}Heq,7a\text{-}H}$ = 7.5 Hz, $^3J_{7\text{-}Heq,6\text{-}H}$ = 3.0 Hz, $^5J_{7\text{-}Heq,4\text{-}H}$ = 1.5 Hz, 1H; 7-H_{eq}), 2.92 (s, 3H; 8-H), 3.13 (dt*, $^3J_{7a\text{-}H,3a\text{-}H}$ = 9.8 Hz, $^3J_{7a\text{-}H,7\text{-}Hax}$ = 9.8 Hz, $^3J_{7a\text{-}H,7\text{-}Heq}$ = 7.5 Hz, 1H; 7a-H), 3.50 (t*, $^3J_{3a\text{-}H,4\text{-}H}$ = 9.8 Hz, $^3J_{3a\text{-}H,7a\text{-}H}$ = 9.8 Hz, 1H; 3a-H), 3.80 (s, 3H; 14-H), 4.12 (m, 1H; 12-H), 4.93 (br d, $^3J_{4\text{-}H,3a\text{-}H}$ = 9.8 Hz, 1H; 4-H), 6.37 ppm (dd, $^3J_{6\text{-}H,7\text{-}Hax}$ = 6.4 Hz, $^3J_{6\text{-}H,7\text{-}Heq}$ = 3.0 Hz, 1H; 6-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 23.1 (C11), 24.9 (C8), 25.0 (C7), 29.2 (C10), 37.3 (C7a), 42.3 (C3a), 52.5 (C14), 52.9 (C4), 61.7 (C12), 117.2 (C5), 132.4 (C6), 170.8 (CO), 174.9 (CO), 175.5 (CO), 178.3 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 386 (1) $[M]^+$, 384 (1) $[M]^+$, 305 (100) $[M-Br]^+$, 194 (36), 84 (42), 77 (21), 44 (13), no further peaks >10%; elemental analysis: calcd (%) for $C_{15}H_{17}{}^{79}BrN_2O_5$: C 46.77, H 4.45, Br 20.74, N 7.27; found: C 46.70, H 4.18, Br 20.51, N 7.15.

10: Methyl 1-(2-methyl-1,3-dioxo-6-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-5-oxopyrrolidine-2-carboxylate, conditions: 110°C, 24 h, silica-gel chromatography, 72% yield. R_f = 0.17 (SiO_2, *n*-heptane/EtOAc = 1:5); m.p.: 138–141°C; IR (nujol): $\tilde{\nu}$ = 3053 (w), 1744 (vs), 1690 (vs), 1340 (m), 1283 (m), 1209 (s), 1135 (m), 1113 (m), 1051 (w), 1014 (m), 988 (w), 973 (w), 952 (w), 811 (w), 798 (w), 768 (m), 721 (w), 706

(m), 682 (w), 661 (w), 590 (w), 569 (w), 512 cm^{-1} (w); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.08–2.18 (m; 1H of CH_2), 2.41–2.55 (m; 2H of CH_2), 2.57–2.70 (m; 2H of CH_2), 2.86 (s, 3H; 8-H), 3.25–3.35 (m, 2H; 1H each of 7a-H and 7-H_{eq}), 3.71 (dd, $^3J_{3a\text{-}H,7a\text{-}H}$ = 9.0 Hz, $^3J_{3a\text{-}H,4\text{-}H}$ = 6.8 Hz, 1H; 3a-H), 3.78 (s, 3H; 14-H), 4.42 (m, 1H; 12-H), 4.93 (ddd, $^3J_{3a\text{-}H,4\text{-}H}$ = 6.8 Hz, $^3J_{4\text{-}H,5\text{-}H}$ = 3.8 Hz, J = 2.0 Hz, 1H; 4-H), 5.85 (m, 1H; 5-H), 7.22–7.34 ppm (m, 5H; Ph); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 25.0 (CH_2), 25.0 (C8), 27.7 (CH_2), 29.6 (CH_2), 39.0 (C7a), 42.0 (C3a), 50.2 (C4), 52.7 (C14), 59.7 (C12), 120.5 (C5), 125.7 (Ph), 128.2 (*p*-Ph), 128.8 (Ph), 139.2, 141.0 (C6, *i*-Ph), 173.9 (CO), 176.0 (CO), 177.4 (CO), 179.0 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 382 (97) $[M]^+$, 355 (32), 350 (10), 326 (64), 295 (100), 266 (85), 255 (12), 240 (39), 182 (15), 169 (10), 155 (97), 144 (14), 128 (46), 115 (26), 105 (11), 91 (11), 84 (21), 77 (40) $[C_6H_5]^+$, 56 (21), 52 (13), 41 (15), 28 (16), no further peaks >10%; HRMS (EI, 70 eV): *m/z* calcd for $C_{21}H_{22}N_2O_5$: 382.1529 $[M]^+$; found: 382.1524.

11: Methyl 1-(2,6-dimethyl-7-(3-methylbut-2-enyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-5-oxopyrrolidine-2-carboxylate, conditions: 110 °C, 24 h, silica-gel chromatography, 38% yield. R_f = 0.14 (SiO_2, *n*-heptane/EtOAc = 1:1); m.p.: 113–114 °C; IR (KBr): $\tilde{\nu}$ = 3433 (s), 3053 (w), 3030 (w), 3001 (w), 2949 (s), 2875 (m), 2844 (w), 1753 (vs), 1687 (vs), 1436 (s), 1412 (s), 1380 (s), 1336 (m), 1313 (m), 1285 (s), 1269 (m), 1242 (m), 1198 (s), 1179 (s), 1157 (m), 1137 (m), 1105 (m), 1071 (w), 1047 (m), 1031 (m), 1017 (m), 989 (m), 976 (m), 964 (m), 925 (w), 893 (w), 874 (w), 834 (w), 805 (m), 791 (m), 766 (m), 741 (m), 685 (m), 633 (m), 623 (m), 603 (m), 586 (w), 572 (w), 545 (w), 520 (w), 501 (w), 470 (w), 456 (w), 412 cm^{-1} (w); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.68 (s, 3H; 20-H), 1.71 (s, 3H; 19-H), 1.72 (s, 3H; 15-H), 2.01–2.11 (m; 1H of 10-H), 2.27 (m, 1H; 7-H), 2.39–2.50 (m, 2H; 1H each of 11-H, 16-H), 2.53–2.66 (m, 2H; 1H each of 10-H, 11-H), 2.82 (m; 1H of 16-H), 2.84 (s, 3H; 8-H), 3.13 (dd, $^3J_{3a\text{-}H,7a\text{-}H}$ = 8.5 Hz, $^3J_{7\text{-}H,7a\text{-}H}$ = 5.3 Hz, 1H; 7a-H), 3.54 (dd, $^3J_{3a\text{-}H,7a\text{-}H}$ = 8.5 Hz, $^3J_{3a\text{-}H,4\text{-}H}$ = 7.5 Hz, 1H; 3a-H), 3.76 (s, 3H; 14-H), 4.26 (m, 1H; 12-H), 4.64 (br, 1H; 4-H), 5.18 (m, 1H; 17-H), 5.31 ppm (br, 1H; 5-H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 18.0 (C20), 19.7 (C15), 24.6 (C8), 24.9 (C10), 25.8 (C19), 26.3 (C16), 29.6 (C11), 40.0 (C7), 41.3 (C7a), 42.3 (C3a), 49.7 (C4), 52.6 (C14), 59.7 (C12), 118.2 (C5), 122.2 (C17), 134.4 (C18), 141.8 (C6), 173.8 (COO), 175.9 (CO), 177.3 (CO), 177.4 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 388 (23) $[M]^+$, 319 (100), 259 (20), 245 (29), 197 (12), 177 (34), 162 (15), 148 (10), 144 (40), 134 (76), 119 (72), 105 (19), 91 (42), 84 (58), 69 (55), 55 (15), 41 (49), no further peaks >10%; HRMS (EI, 70 eV): *m/z* calcd for $C_{21}H_{28}N_2O_5$: 388.1998 $[M]^+$; found: 388.1998.

12: Methyl 1-(2-methyl-6-(4-methylpent-3-enyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-5-oxopyrrolidine-2-carboxylate, conditions: 110 °C, 24 h, silica-gel chromatography, 32% yield. R_f = 0.07 (SiO_2, *n*-heptane/EtOAc = 1:1); IR (neat): $\tilde{\nu}$ = 3454 (s), 3045 (w), 2955 (s), 2917 (s), 2855 (m), 1773 (s), 1740 (vs), 1699 (vs), 1436 (vs), 1411 (s), 1384 (s), 1341 (m), 1283 (s), 1235 (m), 1203 (s), 1145 (m), 1109 (m), 1077 (w), 1048 (m), 1022 (m), 1003 (m), 952 (w), 891 (w), 804 (m), 772 (m), 680 (m), 635 (w), 580 cm^{-1} (m); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.54 (s, 3H; 19-H), 1.63 (brs, 3H; 20-H), 1.83–2.10 (m; 5H of CH_2), 2.21 (m, 1H; 7-H_{ax}), 2.35–2.44 (m; 1H of CH_2), 2.52–2.64 (m; 3H of CH_2), 2.86 (s, 3H; 8-H), 3.12 (ddd, $^3J_{7a\text{-}H,3a\text{-}H}$ = 9.0, 7.7 Hz, J = 1.8 Hz, 1H; 7a-H), 3.58 (dd, $^3J_{3a\text{-}H,7a\text{-}H}$ = 9.0 Hz, $^3J_{3a\text{-}H,4\text{-}H}$ = 6.5 Hz, 1H; 3a-H), 3.74 (s, 3H; 14-H), 4.34 (m, 1H; 12-H), 4.70 (br, 1H; 4-H), 4.90 (m, 1H; 17-H), 5.27 ppm (br, 1H; 5-H); $^3C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 17.8 (C19), 24.9 (C8), 25.0 (C10), 25.6 (CH_2), 25.7 (C20), 28.1 (C7), 29.7 (C11), 37.0 (CH_2), 38.6 (C7a), 41.8 (C3a), 49.3 (C4), 52.6 (C14), 59.7 (C12), 118.0 (C5), 122.9 (C17), 132.4 (C18), 142.0 (C6), 173.9 (COO), 175.9 (CO), 177.6 (CO), 179.2 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 388 (20) $[M]^+$, 319 (100), 291 (11), 263 (11), 259 (28), 245 (13), 234 (15), 231 (11), 178 (14) 144 (26), 119 (10), 92 (30), 84 (43), 69 (52), 56 (10), 41 (45), 28 (13), no further peaks >10%; HRMS (EI, 70 eV): *m/z* calcd for $C_{21}H_{28}N_2O_5$: 388.1998 $[M]^+$; found: 388.1997.

13: Methyl 1-(2-methyl-1,3-dioxo-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1*H*-benzo[*e*]isoindol-4-yl)-5-oxopyrrolidine-2-carboxylate, conditions: 110 °C, 24 h, silica-gel chromatography, 76% yield. R_f = 0.15 (SiO_2, *n*-heptane/EtOAc = 1:5); m.p.: 125–126 °C; IR (nujol): $\tilde{\nu}$ = 3053 (w), 1752 (vs), 1683 (vs), 1336 (w), 1283 (m), 1240 (w), 1196 (m), 1177 (m), 1075 (w), 1047 (m), 1019 (m), 985 (m), 968 (m), 895 (w), 848 (w), 804 (m), 723 (m), 684 (m), 632 (w), 582 (w), 533 cm^{-1} (w); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.36 (m; 1H of 17-H), 1.47 (m; 1H of 16-H), 1.59 (m; 1H of 16-H), 1.71 (m; 1H of 18-H), 1.79–1.88 (m, 2H; 1H each of 17-H, 18-H), 2.01–2.07 (m, 2H; 1H each of 10-H, 15-H), 2.12–2.18 (m; 1H of 15-H), 2.32–2.43 (m, 2H; 1H each of 7-H, 11-H), 2.52–2.61 (m, 2H; 1H each of 10-H, 11-H), 2.87 (s, 3H; 8-H), 3.14 (t*, $^3J_{7a\text{-}H,3a\text{-}H}$ = 8.2 Hz, $^3J_{7a\text{-}H,7\text{-}H}$ = 8.2 Hz, 1H; 7a-H), 3.52 (dd, $^3J_{3a\text{-}H,7a\text{-}H}$ = 8.2 Hz, $^3J_{3a\text{-}H,4\text{-}H}$ = 7.3 Hz, 1H; 3a-H), 3.76 (s, 3H; 14-H), 4.28 (m, 1H; 12-H), 4.86 (m, 1H; 4-H), 5.25 ppm (m, 1H; 5-H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 23.2 (C16), 23.3 (C17), 24.4 (C8), 24.7 (C10), 26.0 (C18), 29.5 (C11), 31.5 (C15), 36.5 (C7), 41.3 (C7a), 42.6 (C3a), 47.9 (C4), 52.5 (C14), 59.6 (C12), 115.5 (C5), 144.5 (C6), 174.1 (C13), 176.1 (C9), 176.9 (CO), 177.3 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 360 (74) $[M]^+$, 332 (40), 305 (12), 301 (19), 273 (49), 249 (61), 244 (32), 217 (68), 190 (39), 162 (13), 144 (46), 132 (43), 117 (14), 112 (12), 106 (26), 91 (100), 84 (72), 79 (24), 77 (17), 65 (11), 56 (25), 41 (20), 28 (12), no further peaks >10%; HRMS (EI, 70 eV): *m/z* calcd for $C_{19}H_{24}N_2O_5$: 360.1685 $[M]^+$; found: 360.1690.

14: Methyl 1-(2-methyl-1,3-dioxo-2,3,3a,3b,4,5,11,11a-octahydro-1*H*-naphtho[2,1-*e*]isoindol-11-yl)-5-oxopyrrolidine-2-carboxylate, conditions: 110 °C, 24 h, silica-gel chromatography, 55% yield. R_f = 0.15 (SiO_2, *n*-heptane/EtOAc = 1:5); m.p.: 170–172 °C; IR (nujol): $\tilde{\nu}$ = 3045 (w), 1743 (vs), 1683 (vs), 1353 (m), 1332 (w), 1290 (m), 1238 (m), 1211 (m), 1179 (m), 1150 (w), 1110 (w), 1086 (w), 1058 (w), 1028 (m), 1009 (w), 989 (m), 948 (w), 892 (w), 850 (m), 805 (w), 773 (w), 753 (s), 670 (w), 645 (w), 595 (w), 559 (w), 515 (m), 466 (w), 451 (w), 419 cm^{-1} (w); ^1H NMR (500 MHz, $CDCl_3$): δ = 2.10–2.18 (m, 2H; 1H each of 10-H, 15-H), 2.27 (m; 1H of 15-H), 2.41–2.49 (m; 1H of 11-H), 2.55–2.73 (m, 4H; 1H each of 7-H, 10-H, 11-H, 16″-H), 2.79 (dt*, $^2J_{16'\text{-}H,16''\text{-}H}$ = 15.1 Hz, $^3J_{15'\text{-}H,16'\text{-}H}$ = 3.5 Hz, $^3J_{15''\text{-}H,16'\text{-}H}$ = 3.5 Hz, 1H; 16′-H), 2.81 (s, 3H; 8-H), 3.24 (dd, $^3J_{7a\text{-}H,3a\text{-}H}$ = 8.8 Hz, $^3J_{7a\text{-}H,7\text{-}H}$ = 7.0 Hz, 1H; 7a-H), 3.75 (dd, $^3J_{3a\text{-}H,7a\text{-}H}$ = 8.8 Hz, $^3J_{3a\text{-}H,4\text{-}H}$ = 6.5 Hz, 1H; 3a-H), 3.78 (s, 3H; 14-H), 4.59 (d*, $^3J_{11'\text{-}H,12\text{-}H}$ = 8.5 Hz, 1H; 12-H), 4.87 (ddd, $^3J_{4\text{-}H,3a\text{-}H}$ = 6.5 Hz, $^3J_{4\text{-}H,5\text{-}H}$ = 3.5 Hz, $^5J_{4\text{-}H,7\text{-}H}$ = 2.2 Hz, 1H; 4-H), 6.05 (t*, $^3J_{5\text{-}H,4\text{-}H}$ = 3.5 Hz, $^4J_{5\text{-}H,7\text{-}H}$ = 3.5 Hz, 1H; 5-H), 7.10 (m, 1H; 17-H), 7.12–7.17 (m, 2H; 18-H, 19-H), 7.29 ppm (m, 1H; 20-H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 24.0 (C15), 24.8 (C8), 24.9 (C10), 29.7 (C11), 29.8 (C16), 36.6 (C7), 42.4 (C7a), 43.3 (C3a), 50.0 (C4), 52.7 (C14), 60.0 (C12), 117.1 (C5), 123.2 (C20), 126.6 (C19), 128.0 (C18), 128.4 (C17), 132.7 (C20a), 138.5 (C16a), 138.7 (C6), 173.9 (C13), 175.9 (C9), 176.7 (CO), 177.2 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 408 (99) $[M]^+$, 380 (25), 352 (75), 321 (43), 292 (100), 265 (83), 236 (11), 208 (10), 194 (12), 180 (59), 165 (38), 154 (73), 141 (20), 137 (21), 128 (26), 115 (18), 89 (11), 84 (18), 56 (13), 41 (13), 28 (13), no further peaks >10%; HRMS (EI, 70 eV): *m/z* calcd for $C_{23}H_{24}N_2O_5$: 408.1685 $[M]^+$; found: 408.1704.

15: Methyl 1-(1,3-dioxo-1,3,3a,4,7,7a-hexahydroisobenzofuran-4-yl)-5-oxopyrrolidine-2-carboxylate, conditions: 110 °C, 24 h, Ac_2O (1.5 equiv), silica-gel chromatography, 82% yield. R_f = 0.36 (SiO_2, *n*-heptane/EtOAc = 1:5); IR (nujol): $\tilde{\nu}$ = 3455 (w), 3364 (w), 3030 (w), 1855 (m), 1771 (vs), 1731 (s), 1689 (vs), 1378 (s), 1348 (m), 1323 (m), 1278 (m), 1220 (s), 1175 (m), 1145 (m), 1107 (m), 1066 (w), 1042 (m), 989 (m), 968 (m), 910 (m), 882 (m), 859 (w), 792 (m), 772 (m), 754 (w), 740 (w), 670 (m), 609 (w), 583 (w), 566 (w), 553 (w), 534 (w), 481 cm^{-1} (w); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.08–2.17 (m; 1H of CH_2), 2.29 (m, 1H; 7-H_{ax}), 2.36–2.46 (m; 1H of CH_2), 2.52–2.62 (m; 2H of CH_2), 2.79 (ddd, $^2J_{7\text{-}Hax,7\text{-}Heq}$ = 16.2 Hz, $^3J_{6\text{-}H,7\text{-}Heq}$ = 6.9 Hz, $^3J_{7a\text{-}H,7\text{-}Heq}$ = 1.9 Hz, 1H; 7-H_{eq}), 3.48 (ddd, $^3J_{7a\text{-}H,3a\text{-}H}$ = 9.9 Hz, $^3J_{7a\text{-}H,7\text{-}Hax}$ = 8.0 Hz, $^3J_{7a\text{-}H,7\text{-}Heq}$ = 1.9 Hz, 1H; 7a-H), 3.77 (s, 3H; 13-H), 3.96 (dd, $^3J_{3a\text{-}H,7a\text{-}H}$ = 9.9 Hz, $^3J_{3a\text{-}H,4\text{-}H}$ = 7.0 Hz, 1H; 3a-H), 4.34 (m, 1H; 11-H), 4.76 (m, 1H; 4-H), 5.80 (dt*, $^3J_{5\text{-}H,6\text{-}H}$ = 9.8 Hz, $^3J_{4\text{-}H,5\text{-}H}$ = 3.2 Hz, $^4J_{5\text{-}H,7\text{-}Hax}$ = 3.2 Hz, 1H; 5-H), 6.09 ppm (m, 1H; 6-H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 23.9 (C7), 24.9 (CH_2), 29.4 (CH_2), 38.9 (C7a), 42.5 (C3a), 48.1 (C4), 52.8 (C13), 59.3 (C11), 126.3 (C5), 129.6 (C6), 171.2 (CO), 173.4 (CO), 173.4 (COO), 176.2 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 293 (6) $[M]^+$, 234 (52) $[M-C_2H_3O_2]^+$, 195 (21), 136 (37), 84 (100), 79 (40), 77 (30), 69 (10), 53 (10), 41 (24), 28 (39), no further peaks >10%; HRMS (ESI): *m/z* calcd for $C_{14}H_{16}NO_6$: 294.0978 $[M+H]^+$; found: 294.0973.

16: Diethyl 3-(2-(methoxycarbonyl)-5-oxopyrrolidin-1-yl)-6-methylcyclohexa-1,4-diene-1,2-dicarboxylate, conditions: 110 °C, 24 h, dienophilic acetylenedicarboxylate (5 equiv), silica-gel chromatography, 65% yield. **16a**: R_f = 0.10 (SiO_2, *n*-heptane/EtOAc = 1:1); IR (neat): $\tilde{\nu}$ = 3468 (w), 2981 (s), 2932 (m), 2906 (m), 2886 (w), 1724 (vs), 1643 (m), 1439 (m), 1404 (s), 1368 (m), 1339 (w), 1256 (vs), 1203 (s), 1179 (s), 1095 (m), 1068 (m), 1050 (m), 1020 (m), 992 (m), 894 (w), 862 (m), 819 (w), 780 (m), 749 (w), 717 (w), 667 (w), 597 (w), 553 cm^{-1} (w); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.20 (d, ^3J = 7.3 Hz, 3H; 20-H), 1.24 (t, ^3J = 7.3 Hz, 3H; CH_3CH_2), 1.28 (t, ^3J = 7.3 Hz, 3H; CH_3CH_2), 1.92–1.98 (m; 1H of 10-H), 2.25–2.36 (m, 2H; 1H each of 9-H, 10-H), 2.57–2.65 (m; 1H of 9-H), 3.19 (m, 1H; 6-H), 3.66 (s, 3H; 13-H), 4.10 (dd, $^3J_{11\text{-}H,10'\text{-}H}$ = 9.1 Hz, $^3J_{11\text{-}H,10''\text{-}H}$ = 1.5 Hz, 1H; 11-H), 4.12–4.20 (m, 2H; CH_3CH_2), 4.23 (q, J = 7.3 Hz, 2H; CH_3CH_2), 5.46 (ddd, $^3J_{4\text{-}H,5\text{-}H}$ = 10.0 Hz, $^3J_{4\text{-}H,3\text{-}H}$ = 4.0 Hz, $^4J_{4\text{-}H,6\text{-}H}$ = 1.5 Hz, 1H; 4-H), 5.64 (ddd, $^5J_{3\text{-}H,6\text{-}H}$ = 6.3 Hz, $^3J_{3\text{-}H,4\text{-}H}$ = 4.0 Hz, $^4J_{3\text{-}H,5\text{-}H}$ = 1.5 Hz, 1H; 3-H), 5.78 ppm (ddd, $^3J_{5\text{-}H,4\text{-}H}$ = 10.0 Hz, $^3J_{5\text{-}H,6\text{-}H}$ = 4.0 Hz, $^4J_{5\text{-}H,3\text{-}H}$ = 1.5 Hz, 1H; 5-H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 13.9 (CH_3CH_2), 14.0 (CH_3CH_2), 19.7 (C20), 24.0 (C10), 29.5 (C9), 31.4 (C6), 47.0 (C3), 52.0 (C13), 56.7 (C11), 61.4 (CH_3CH_2), 61.5 (CH_3CH_2), 120.9 (C4), 131.7 (C2), 133.7 (C5), 139.8 (C1), 166.1 (CO), 166.9 (CO), 173.5 (C12), 175.2 ppm (C8); MS (EI, 70 eV): *m/z* (%) = 379 (1) $[M]^+$, 334 (28) $[M-C_2H_5O]^+$, 318 (75), 290 (42), 260 (23), 230 (84), 223 (11), 202 (35), 191 (100), 177 (15), 163 (87), 149 (31), 144 (14), 137 (16), 119 (32), 91 (39), 84 (52), 77 (20), 65 (18), 56 (13), 42 (20), 29 (94), no further peaks >10%; HRMS (EI, 70 eV): *m/z* calcd for $C_{19}H_{25}NO_7$: 379.1631 $[M]^+$; found: 379.1635. **16b**: R_f = 0.08 (SiO_2, *n*-heptane/EtOAc = 1:1); IR (neat): $\tilde{\nu}$ = 3443 (m), 2982 (s), 2932 (m), 2907 (m), 2880 (w), 1732 (vs), 1642 (m), 1440 (m), 1403 (s), 1368 (m), 1258 (vs), 1182 (m), 1106 (m), 1075 (m), 1049 (m), 1021 (m), 991 (w), 863 (m), 791 (w), 739 (w), 648 (w), 547 cm^{-1} (w); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.26 (d, ^3J = 7.3 Hz, 3H; 20-H), 1.27 (t, ^3J = 7.3 Hz, 3H; CH_3CH_2), 1.31 (t, ^3J = 7.3 Hz, 3H; CH_3CH_2), 1.99 (m, 1H; 10″-H), 2.18–2.27 (m, 1H; 10′-H), 2.35 (ddd, $^2J_{9'\text{-}H,9''\text{-}H}$ = 16.4 Hz, $^3J_{9''\text{-}H,10\text{-}H}$ = 9.5 Hz, $^3J_{9''\text{-}H,10\text{-}H}$ = 1.9 Hz, 1H; 9″-H), 2.61 (ddd, $^2J_{9'\text{-}H,9''\text{-}H}$ = 16.4 Hz, $^3J_{9'\text{-}H,10\text{-}H}$ = 11.0 Hz, $^3J_{9'\text{-}H,10\text{-}H}$ = 9.5 Hz, 1H; 9′-H), 3.10 (m, 1H; 6-H), 3.69 (s, 3H; 13-H), 4.07 (dd, $^3J_{11\text{-}H,10'\text{-}H}$ = 9.5 Hz, $^3J_{11\text{-}H,10''\text{-}H}$ = 1.5 Hz, 1H; 11-H), 4.09–4.16 (m; 1H of CH_3CH_2), 4.22–4.34 (m; 3H of CH_3CH_2), 5.44 (ddd, $^3J_{4\text{-}H,5\text{-}H}$ = 9.8 Hz, $^3J_{4\text{-}H,3\text{-}H}$ = 4.2 Hz, $^4J_{4\text{-}H,6\text{-}H}$ = 1.3 Hz, 1H; 4-H), 5.76 (ddd, $^5J_{3\text{-}H,6\text{-}H}$ = 5.7 Hz, $^3J_{3\text{-}H,4\text{-}H}$ = 4.2 Hz, $^4J_{3\text{-}H,5\text{-}H}$ = 1.3 Hz, 1H; 3-H), 5.96 ppm (ddd, $^3J_{5\text{-}H,4\text{-}H}$ = 9.8 Hz, $^3J_{5\text{-}H,6\text{-}H}$ = 5.0 Hz, $^4J_{5\text{-}H,3\text{-}H}$ = 1.3 Hz, 1H; 5-H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 14.0 (CH_3CH_2), 14.1 (CH_3CH_2), 18.6 (CH_3), 24.1 (C10), 29.9 (C9), 33.9 (C6), 45.2 (C3), 52.5 (C13), 56.4 (C11), 61.2 (CH_3CH_2), 61.3 (CH_3CH_2), 121.3 (C4), 123.7 (C2), 133.6 (C5), 148.7 (C1), 164.2 (CO), 168.8 (CO), 172.9 (CO), 174.3 ppm (C8); MS (EI, 70 eV): *m/z* (%) = 379 (1) $[M]^+$, 333 (13) $[M-C_2H_6O]^+$, 318 (100), 290 (10), 260 (12), 230 (19), 216 (12), 191 (60), 163 (69), 149 (22), 119 (12), 91 (12), 84 (49), 41 (11), no further peaks >10%; HRMS (EI, 70 eV): *m/z* calcd for $C_{19}H_{25}NO_7$: 379.1631 $[M]^+$; found: 379.1615.

17: Methyl 1-(6-cyanocyclohex-2-enyl)-5-oxopyrrolidine-2-carboxylate, conditions: 140 °C, 3 days, dienophilic acrylonitrile (3 equiv), silica-gel chromatography, 35% yield. R_f = 0.11 (SiO_2, *n*-heptane/EtOAc = 1:1); IR (neat): $\tilde{\nu}$ = 3614 (w), 3468 (m), 3386 (m), 3038 (m), 2955 (s), 2845 (m), 2240 (m), 1747 (vs), 1694 (vs), 1436 (s), 1406 (vs), 1340 (m), 1283 (s), 1209 (vs), 1147 (m), 1089 (w), 1069 (w), 1046 (m), 1027 (m), 988 (m), 967 (m), 910 (w), 878 (w), 811 (m), 778 (m), 744 (m), 681 (m), 608 (w), 571 (m), 539 (w), 483 cm^{-1} (w); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.88–2.12 (m, 4H; 1H each of 4″-H, 5′-H, 5″-H, 9″-H), 2.34–2.58 (m, 4H; 1H each of 4′-H, 9′-H, 10′-H, 10″-H), 3.44 (m, 1H; 6-H), 3.76 (s, 3H; 13-H), 4.54 (d, ^3J = 8.5 Hz, 1H; 11-H), 4.90 (m, 1H; 1-H), 5.41 (m, 1H; 2-H), 5.98 ppm (m, 1H; 3-H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 21.6 (C4), 23.6 (C5), 25.2 (C9), 29.3 (C10), 30.2 (C6), 48.4 (C1), 52.6 (C13), 58.4 (C11), 119.6 (C14), 121.7 (C2), 132.3 (C3), 173.4 (C12), 176.0 ppm (C8); MS (EI, 70 eV): *m/z* (%) = 248 (33) $[M]^+$, 221 (39), 195 (73), 189 (38) $[M-C_2H_3O_2]^+$, 162 (12), 136 (71), 108 (18), 105 (14), 93 (10), 84 (100), 79 (20), 57 (11), 54 (10), 42 (26), 28 (51), no further peaks >10%; HRMS (EI, 70 eV): *m/z* calcd for $C_{13}H_{16}N_2O_3$: 248.1161 $[M]^+$; found: 248.1159.

18: 4,10-Dimethyl-1,2,3,4,-tetrahydronaphtalene-[2,1-*m*]-4,10-diazatetracyclo[5.5.2.$0^{2,6}$.$0^{8,12}$]tetradec-13-ene-3,5,9,11-tetrone, conditions: 110 °C, 24 h, silica-gel chromatography, 14% yield. R_f = 0.14 (SiO_2, *n*-heptane/EtOAc = 1:1); m.p.: 249 °C; IR (KBr): $\tilde{\nu}$ = 3441 (m), 3071 (m), 3038 (w), 2947 (m), 2903 (m), 2868 (w), 1769 (s), 1701 (vs), 1489 (m), 1437 (vs), 1381 (s), 1313 (s), 1292 (vs), 1226 (m), 1210 (m), 1178 (w), 1148 (m), 1130 (m), 1078 (m), 1054 (m), 998 (m), 984 (m), 971 (s), 926 (w), 875 (m), 824 (m), 806 (w), 775 (s), 761 (vs), 731 (w), 711 (w), 654 (m), 641 (m), 628 (m), 611 (w), 590 (m), 450 (m), 429 (m), 407 cm^{-1} (m); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.78 (s, 6H; NCH_3), 2.81–2.95 (m, 6H; 2H of COCH, 4H of CH_2), 3.07 (dd, J = 8.1, 3.0 Hz, 2H; 2H of COCH), 3.92 (dt, J = 6.4, 3.0 Hz, 1H; C=CHC*H*), 6.47 (d, J = 6.4 Hz, 1H; C=C*H*CH), 7.03–7.18 (m; 3H of CH_{arom}), 7.25–7.29 ppm (m; 1H of CH_{arom}); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ = 24.9 (2NCH_3), 25.7 (CH_2), 26.6 (CH_2), 33.4 (C=CH*C*H), 42.5 (C), 44.9 (2CO*C*H), 48.9 (2CO*C*H), 119.1 (C=*C*H), 123.2 (CH_{arom}), 126.3 (CH_{arom}), 128.7 (2CH_{arom}), 130.3 (*C*=CH), 137.3 (C_{arom}), 139.0 (C_{arom}), 175.9 (2CO), 176.4 ppm (2CO); MS (EI, 70 eV): *m/z* (%) = 376 (100) $[M]^+$, 264 (74), 179 (70), 165 (12), 113 (28), 59 (15), 28 (15), no further peaks >10%; HRMS (EI, 70 eV): *m/z* calcd for $C_{22}H_{20}N_2O_4$: 376.1418 $[M]^+$; found: 376.1400.

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