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In Situ Generation of Chiral *N*-Dienyl Lactams in a Multicomponent Reaction: An Efficient and Highly Selective Way to Asymmetric Amidocyclohexenes

Sandra Hübner, Haijun Jiao, Dirk Michalik, Helfried Neumann, Stefan Klaus, Dirk Strübing, Anke Spannenberg, and Matthias Beller*[a]

Dedicated to Prof. Dr. Bernhard Lücke on the occasion of his 70th birthday

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 on a highly efficient and diastereoselective multicomponent methodology utilizing chiral **a**mides, **a**ldehydes, and **d**ienophiles (AAD reaction). The three components readily react under in situ generation of chiral *N*-dienyl lactams which undergo a subsequent Diels–Alder reaction. Different chiral amides have been employed in the standard protocol delivering yields up to 94%, and selectivities up to 90% *de*. Moreover, DFT calculations were performed to explain the obtained selectivities.

Keywords: cyclohexenes · density functional theory · diastereoselectivity · Diels–Alder reactions · multicomponent reactions

Introduction

Multicomponent reactions (MCRs) offer significant advantages over stepwise procedures,[1] especially with respect to environmental sustainability, practicability, and atom efficiency.[2] Compared to stepwise procedures, the most evident benefit of multicomponent reactions lies in the inherent formation of several bonds in one operation without isolation of the intermediates, changing the reaction conditions, or addition of any further reagents. Historically significant examples 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 tremendously rich multicomponent chemistry. Thus, multicomponent methodologies prove to be an effective tool in organic synthesis. However, the demand for diversified, time- and cost-efficient syntheses of bioactive compounds and natural products in order to establish substance libraries still exists.

A few years ago, we discovered a new multicomponent method in which **a**mides and **a**ldehydes react with **d**ienophiles (AAD reaction) to give a large variety of 1-acylamino-2-cyclohexene derivatives in unprecedented efficiency.[10–14] The AAD reaction involves 1-(*N*-acylamino)-1,3-butadienes as key intermediates, which are generated in the initial condensation step and trapped by dienophiles in a subsequent Diels–Alder reaction (Scheme 1).

By utilization of simple aliphatic and aromatic aldehydes the substitution of the diene backbone is limited to the 2 and 4 positions only, owing to 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 along the 1,3-butadiene backbone and hence significantly increases the substrate diversity (Scheme 1, bottom).[12] A special feature of the AAD reaction is the tolerance of a large variety of amides. Not only simple or substituted acetamides and benzamides, but also ureas, sulfonamides, and carbamates can be employed in this one-pot reaction. Typically, reactive

[a] S. Hübner, Dr. H. Jiao, Dr. D. Michalik, Dr. H. Neumann, S. Klaus, Dr. D. Strübing, Dr. A. Spannenberg, Prof. Dr. M. Beller
Leibniz-Institut für Katalyse e.V. an der
Universität Rostock
Albert-Einstein-Strasse 29a, 18059 Rostock (Germany)
Fax: (+49) 381-1281-5000
E-mail: Matthias.Beller@catalysis.de

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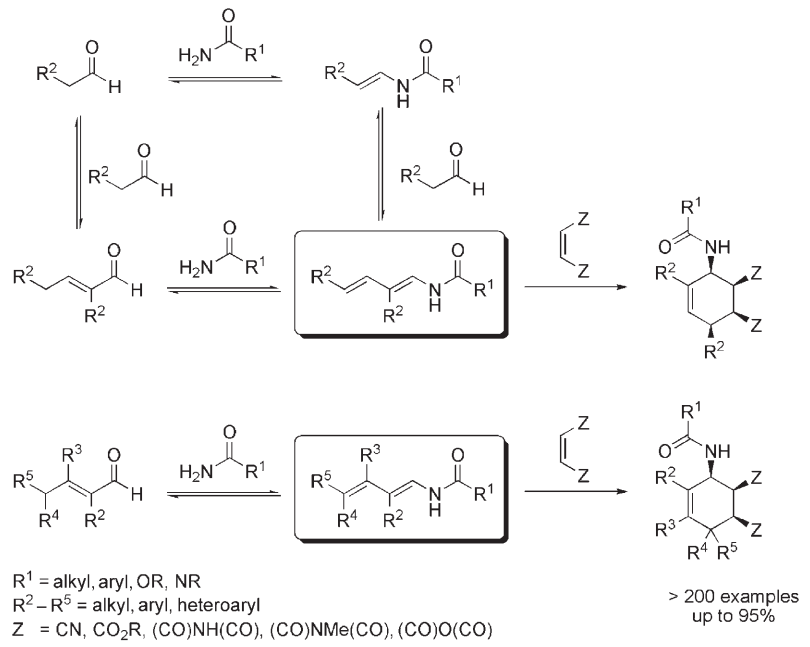


Scheme 1. General reaction scheme of the **a**ldehyde–**a**mide–**d**ienophile multicomponent reaction (AAD MCR).

dienophiles such as maleimide, *N*-methylmaleimide, acrylonitrile, maleic anhydride, tetracyanoethylene, and acrylic acid esters have to be applied in the Diels–Alder step.[13,14] Furthermore, in most cases, an all-*syn* configuration along the cyclohexene ring was observed in the resulting AAD MCR products owing to the selective *endo* addition of the dienophiles. In the course of the AAD reaction sequence, up to four stereogenic centers are generated, and only one diastereomer is isolated as a racemic mixture in most cases, which already proves the high selectivity of our one-pot procedure (Scheme 1). The importance of Diels–Alder chemistry to natural product synthesis has directed our attention to the development of a stereoselective variant of this MCR.

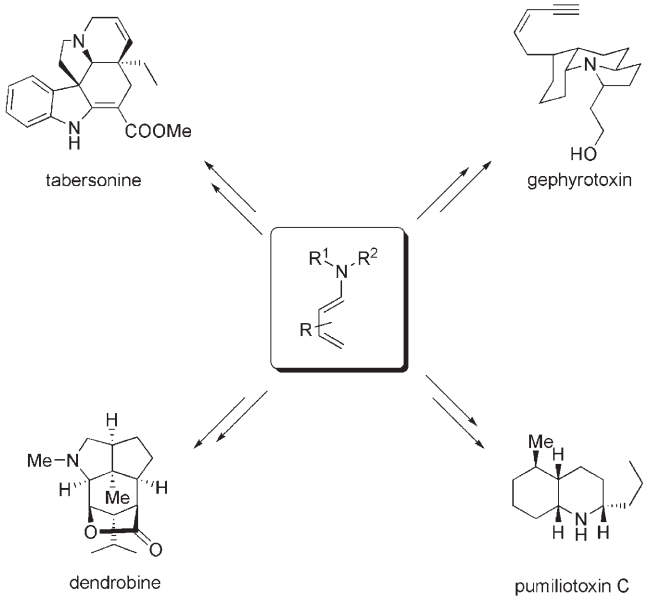
Chiral Dienamides in Diels–Alder and Multicomponent Reactions

A number of groups have demonstrated the synthetic versatility of 1-acylamino-1,3-dienes for Diels–Alder chemistry.[15,16] Prominent examples in which aminodiene-based Diels–Alder reactions constitute attractive solutions for the formation of six-membered carbocycles with high regio- and stereoselectivity include the total syntheses of tabersonine,[17] gephyrotoxin,[18] dendrobine,[19] and pumiliotoxin C[20] (Scheme 2).

So far, several synthetic approaches to Oppolzer–Overman-type dienes and related 1-acylamino-1,3-butadiene derivatives have been presented in the literature.[21] In 1999, Barluenga et al.[22] published a review on the synthesis of chiral heterosubstituted 1,3-butadienes and their application in [4+2] cycloadditions which gives a broad overview on this chemistry until the late 1990s. Herein, we concentrate on chiral *N*-dienyl lactams as key intermediates for diastereoselective Diels–Alder reactions.

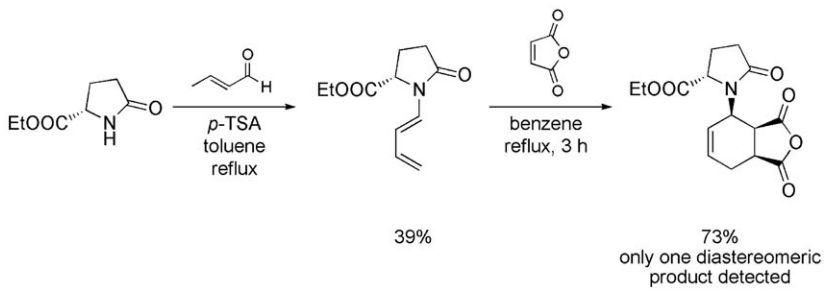
The first synthesis of an asymmetric *N*-dienyl lactam was developed by Smith and co-workers employing (*S*)-ethyl pyroglutamate and crotonaldehyde.[23] The corresponding diene was obtained in 39% yield and reacted with maleic anhydride in a second step to give one diastereomeric product in 73% yield (Scheme 3).

Later on, chiral oxazolidin-2-one-substituted dienes were investigated in Diels–Alder reactions. In this case, Stevenson and co-workers reported the

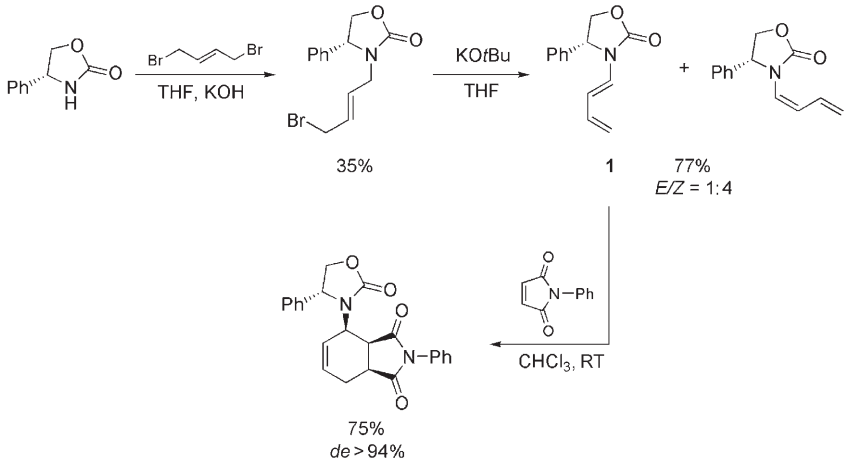


Scheme 2. Aminodienes as building blocks in natural product syntheses.

preparation of 3-(buta-1,3-dienyl)-4-phenyloxazolidin-2-one (**1**) and its subsequent utilization in a cycloaddition with *N*-phenylmaleimide (Scheme 4).[24] Although the diastereoselectivity was convincing (>94% *de*), again the difficulty of this chemistry is illustrated by the multistep synthesis of the *N*-dienyl lactam, which turned out to be a major drawback of this strategy. The group presented three approaches to the desired dienamide.[25] One is depicted in Scheme 4 and gave a 4:1 mixture of *Z* to *E* dienamide. Unfortunately, only the minor *E* isomer shows reactivity in Diels–Alder reac-



Scheme 3. The first synthesis of an asymmetric *N*-dienyl lactam by Smith and co-workers. *p*-TSA = *p*-toluenesulfonic acid.



Scheme 4. Preparation of 3-(buta-1,3-dienyl)-4-phenyloxazolidin-2-one (**1**) and subsequent application in Diels–Alder reactions by Stevenson et al.

tions. A second approach involved Wittig chemistry and gave low yields (24%); again the undesired *Z* isomer was obtained as the major product. Although a third reaction sequence delivered the *E* isomer, it entailed five steps. However, utilization of isopropyloxazolidinone and 3-methylisoindolinone afforded the corresponding *N*-dienyl lactams by simple condensation with crotonaldehyde. In Diels–Alder reactions the dienamides exhibited high selectivities, comparable to that of the asymmetric phenyl-substituted *N*-dienyl lactam **1**.[25]

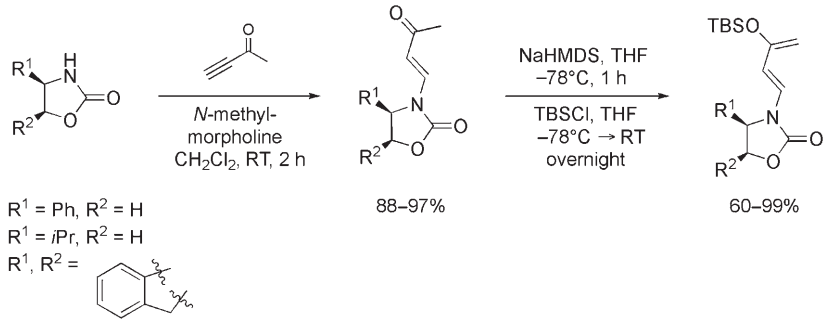
Dienamide **1** has also been adopted successfully for the [4+2] cycloaddition with 2-substituted vinylphosphonates.[26] The reaction was further improved by utilizing a phenyl-substituted oxazolidin-2-thionyl diene.[27] It was found that substitution of the oxygen atom by a sulfur atom increases the facial selectivity of the diene.

Chiral Danishefsky-type amido siloxy dienes have been prepared by Rawal et al.[16] Treatment of the differently substituted oxazolidinones with 3-butyn-2-one gave the corresponding vinylogous amides in 88–97% yield. Reaction with NaHMDS and subsequent silylation with TBSCl delivered the targeted dienes (Scheme 5).

The aforementioned procedures clearly represent the versatility and high selectivity of chiral *N*-dienyl lactams in asymmetric Diels–Alder reactions. However, multistep syntheses and/or moderate yields of the targeted amino dienes definitely lower their synthetic value. Asymmetric Diels–Alder-based MCRs and domino reactions have been reviewed by Yus and Ramón,[28] and by Pellissier[29] very recently, but to the best of our knowledge in situ generation of chiral *N*-dienyl lactams has not been reported in the literature so far.

The principle of introducing chiral information through one of the three starting substances of our AAD MCR has already been proven by our group.[13] One-pot reactions with chiral dienophilic α,β-unsaturated *N*-acyl oxazolidinones[30] followed by cleavage[31] of the auxiliary afforded the desired 1-*N*-acylaminocyclohexene-2-carboxylates with moderate yields but excellent stereoselectivities (>90% *ee*).[13] Kessler and co-workers successfully applied this strategy to their work on the synthesis of somatostatin analogs (Scheme 6).[32] The group employed chiral dienophilic acrylates and attained diastereoselectivities of up to 92% *de*. Unfortunately, the yields were again only moderate (around 30%).

Herein we report the introduction of the chiral information through the amide component. Hence, diastereomers are generated instead of racemic product mixtures. As in



Scheme 5. Synthesis of amido siloxy dienes as reported by Rawal et al. HMDS = hexamethyldisilazide, TBS = *tert*-butyldimethylsilyl.

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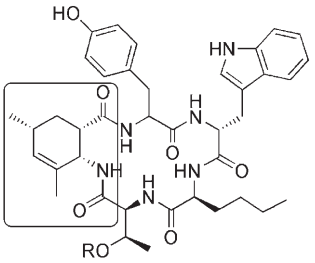


Scheme 6. *Somatostatin* analogues synthesized by Kessler and co-workers on the basis of the AAD-MCR. The typical AAD product pattern is framed.

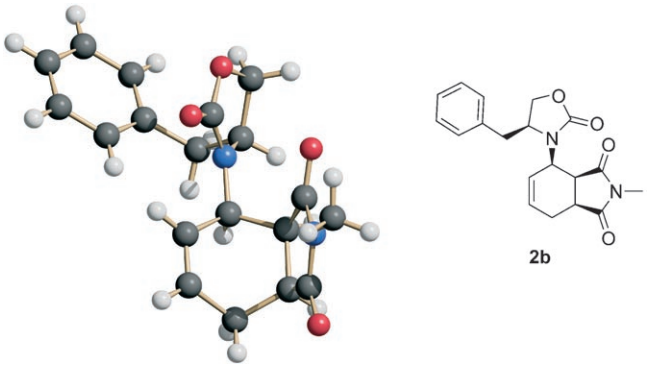


Figure 1. Crystal structure of the minor diastereomer (3a*S*,4*R*,7a*S*)-4-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-2-methyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (**2b**).

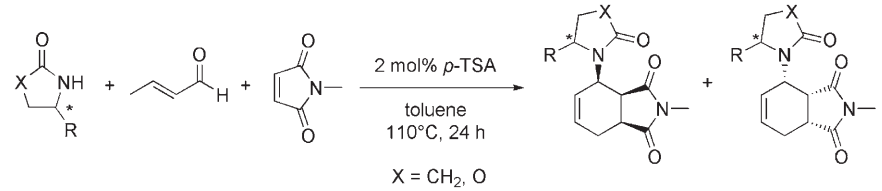
the non-asymmetric AAD MCR, the *endo* selectivity throughout the Diels–Alder step should dictate the stereochemical outcome of the reaction and, in principle, diastereoselective induction should easily be achieved by differentiation of the two faces of the diene, assuming that the dienophile approaches from the less-hindered side. Thus, only two diastereomers are conceivable (see Scheme 7). In the following only the major diastereomer will be pictured.

Results and Discussion

Does Temperature Matter? — Looking for Optimal Conditions

We started our investigations with the utilization of the benzyl-substituted oxazolidinone in a model reaction. As expected, two diastereomers of the corresponding AAD MCR product **2** were formed (Scheme 7, R = Bn, X = O) which were separated easily by flash column chromatography, and, fortunately, the minor diastereomer **2b** crystallized (Figure 1). The X-ray data do not allow any statements concerning the absolute configuration, but clearly the relative configuration can be deduced. Hence, provided that the stereogenic center at the oxazolidinone moiety does not racemize in the course of the reaction, the structure of the minor diastereomer **2b** can be determined as presented in Figure 1.

On the basis of the X-ray crystal structure of the minor diastereomer **2b** and the NMR spectroscopic data, the stereochemistry of the two diastereomers of compound **2** could be established. Figure 2 shows parts of the ^{1}H NMR spectra of the pure major diastereo-



Scheme 7. Diastereoselective variant of the AAD-MCR by introduction of chiral information *via* the amide.

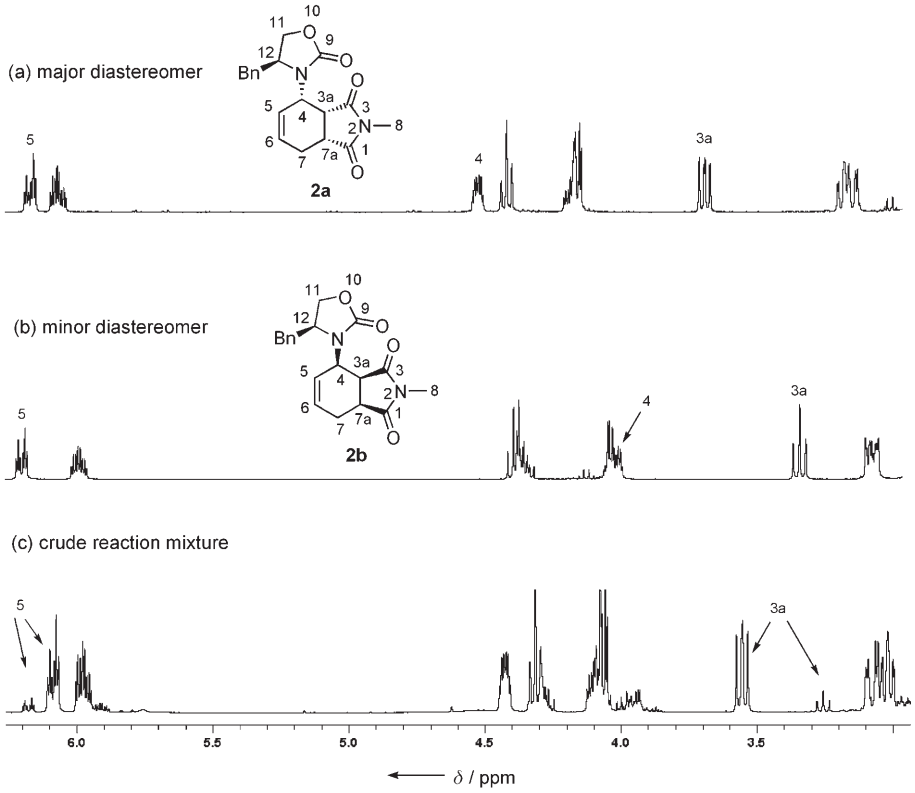


Figure 2. Region of the ^{1}H NMRs of (a) the pure major diastereomer **2a**, (b) the pure minor diastereomer **2b**, (c) the crude reaction mixture of compound **2**.

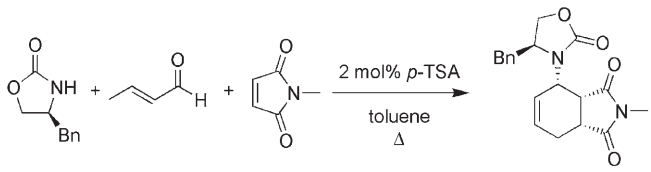
mer **2a** (Figure 2a), the pure minor diastereomer **2b** (Figure 2b), and the corresponding region of the crude reaction mixture of compound **2** containing both diastereomers **2a** and **2b** (Figure 2c). The signals for 3a-H and 4-H for the major diastereomer **2a** were shifted downfield relative to those for the minor diastereomer **2b**, and the respective coupling constant $^3J_{3a,4}$ is approximately 2 Hz smaller. Further investigations showed that this is also true for all AAD products published herein. Hence, the chemical shifts for 3a-H and 4-H as well as the vicinal coupling constants can generally be used as indicators for the determination of the major and minor diastereomers. The conformation of the cyclohexene ring of fused five- and six-membered ring skeletons has already been studied extensively on similar compounds.[33] To investigate the conformation of our compounds, we have taken the 2D ^{1}H,^{1}H-NOESY NMR spectra of **2** and **3**. In the NOESY spectra for both diastereomers of **2** and **3** correlations were found for 4-H and 7-H_{ax}, thus proving that the six-membered ring appears in a boat-shaped concave conformation with the substituent on the nitrogen atom in the equatorial orientation.

The signals of the corresponding 3a-H and 5-H of the two diastereomers **2a** and **2b** significantly differ in their chemical shift value (Figures 2a and b). This is also true for the ^{1}H NMR spectrum of the crude reaction mixture (Figure 2c). We therefore decided to determine the diastereoselectivities by ^{1}H NMR spectroscopy simply by integrating the signals for the corresponding protons. Advantageously, in this case a calibration of the diastereomers was not necessary.

Next, we investigated whether a change in the reaction parameters would have any influence on the stereochemical outcome of the conversion. For this purpose, a number of experiments were performed on a 0.5-mmol scale. The diastereoselectivities were determined by ^{1}H NMR spectroscopy as described above. The results are outlined in Table 1. The denoted yields comprise both isomers and were also determined by the ^{1}H NMR spectra with hexadecane as internal standard.

In agreement with previous experiments, AAD products are obtained in the highest yields when the reaction is carried out at a temperature of 110 °C, for about 24 h with 2 mol% of *p*-TSA in toluene with a slight excess of aldehyde, and acetic acid anhydride as the water-removing agent (Table 1, entry 2). Initially, the necessity of the additive was studied. It showed that the addition of Ac_2O did not have a significant impact on the diastereoselectivity (Table 1, entries 1 and 2; 73 and 74% *de*, respectively). All further experiments were run without a water-removing agent, although a slightly better yield was obtained in the presence of Ac_2O (Table 1, entries 1 and 2, 91% and 99%). In general, a decrease in the reaction temperature results in improved diastereoselectivity in the Diels–Alder reactions. However, when the temperature was decreased to 80 °C, the product was only obtained in lower yield (84%), and the diastereomeric excess remained at 75% (Table 1, entry 3). We then investigated whether there is a change in stereoselectivity with time (Table 1, entries 4 and 5). Evidently, the reaction needs longer reaction times, as the products were obtained in yields of 60% and 77%, respectively. Once again we did not observe any effect on the diastereoselectivity (73% *de* in both cases). The same is true for different amounts of aldehyde, and a change in concentration (Table 1, entries 6–8, 74% *de* in all cases). Clearly the diastereoselectivity seems to be independent of time, concentration, and temperature. Nevertheless, the results clearly show that excess aldehyde is required to allow good yields (compare Table 1, entries 6, 1, and 7 with 78%, 91%, and 96% yield, respectively). Moreover, to simplify matters, acetic acid anhydride can be omitted in this procedure.

Table 1. Table 1
Influence of critical parameters.



Entry	Aldehyde (equiv)	T [°C]	t [h]	Conc. [mmol mL^{-1}]	*de* [%][a]	Yield [%][b]
1	1.5	110	24	0.125	73	91
2	1.5[c]	110	24	0.125	74	99
3	1.5	80	24	0.125	75	84
4	1.5	110	3	0.125	73	60
5	1.5	110	6	0.125	73	77
6	1.0	110	24	0.125	74	78
7	2.0	110	24	0.125	74	96
8	1.5	110	24	0.25	74	96

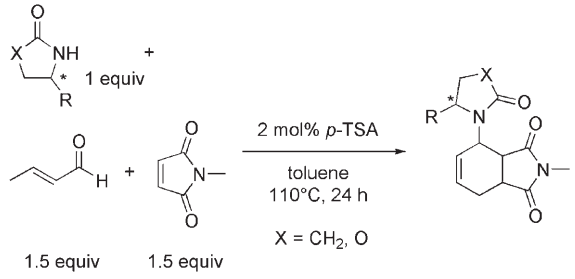
[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture with hexadecane as internal standard. [c] Addition of Ac_2O (1 equiv).

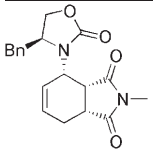
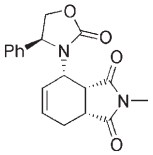
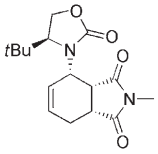
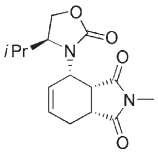
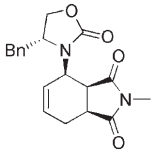
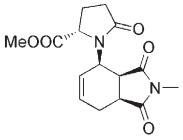
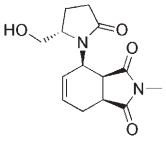
Does Size Matter? — Various Amides in Comparison

We then concentrated on the variation of the chiral amide component. Apparently, it is reasonable to test differently substituted Evans-type oxazolidinones. To determine the yields of the isolated products, preparative experiments were performed on a 3-mmol scale. Again *de* values were determined from the crude reaction mixtures of smaller-scale reactions (0.5 mmol). The results are summarized in Table 2.

Generally, the corresponding AAD MCR products were obtained in excellent yields (77–94%). Clearly, this is a substantial advantage over previously reported methods.[13,32] While studying various chiral auxiliaries it turned out that ^{1}H NMR spectroscopy is not always suitable for the determination of the diastereoselectivities owing to overlapping signals. For example, in case of the AAD product **8** the diastereoselectivity was measured by HPLC analysis. In the case of compounds **3** and **7**, ^{13}C NMR spectroscopy (inverse gated decoupling = IG) was employed for the integration of ^{13}C signals. Thus, the diastereoselectivities were determined

Table 2. Comparison of various amides in the reaction.

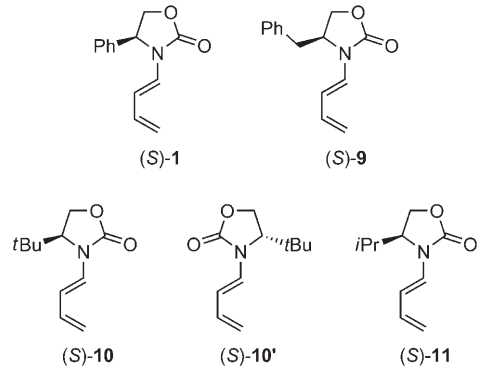


Amides		Yield[a] [%]	*de* [%]
	**2**	89	74[b], 75[c]
	**3**	94	90[c]
	**4**	87	75[b]
	**5**	92	85[b]
	**6**	92	75[b]
	**7**	77	74[c]
	**8**	84	<15[d]

[a] Yields of isolated products. The diastereoselectivities were determined from the crude reaction mixtures by: [b] ^{1}H NMR; [c] ^{13}C NMR (inverse gated decoupling); [d] HPLC.

to be 90% *de* for the phenyl-substituted derivative **3** and 74% *de* for the pyroglutamate derivative **7**. To back up the method, the benzyl substituted AAD-MCR product **2** was investigated again by ^{13}C NMR spectroscopy (IG), the data from which (75% *de*) matched that obtained by ^{1}H NMR method (74% *de*). When (*R*)-4-benzyl-2-oxazolidinone was utilized in the AAD MCR instead of the *S* enantiomer, the corresponding product **6** was formed with a diastereoselectivity of 75% *de*. The NMR data for the isolated pair of diastereomers is consistent with those for the isomeric pair **2**, indicating that major **6a** is the corresponding enantiomer to major **2a**. Of course, the same is true for the minor isomers **6b** and **2b**.

As expected, the obtained structural and analytical data indicate that the dienophile approaches the dienamide from the less-hindered side in the Diels–Alder step. As already stated, the diastereoselectivity is induced by differentiation of the two faces of the diene. Surprising is the relatively high selectivity at temperatures of 110°C. To understand these selectivity issues throughout the Diels–Alder step, we carried out high-level B3LYP density-functional-theory calculations. In these studies, we concentrated on the reactions of the substituted *N*-dienyl oxazolidinones (Scheme 8) with *N*-methylmaleimide.



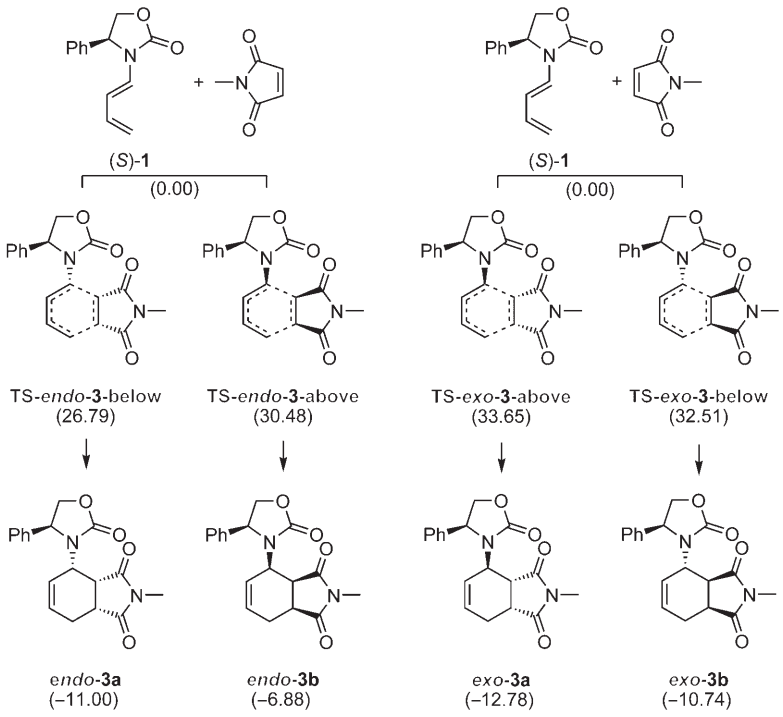
Scheme 8. Calculated substituted *N*-dienyl oxazolidin-2-ones.

As diastereoselectivity results from the relative position of the dienophile to the diene, that is, the dienophile can stand above or below the diene, we have used the notation "above" and "below" to distinguish the addition modes. 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.

First, we were interested in the phenyl-substituted oxazolidinone derivative (*S*)-3-(buta-1,3-dienyl)-4-phenyloxazolidin-2-one (**1**, Scheme 8), which gave the highest selectivity (90% *de*). Notably, **1**, **9**, and **11** are the more-stable conformers, and the conformers **1′**, **9′**, and **11′** with the oxazolidinone group rotated by approximately 180° are higher in energy by 2.04, 2.23, and 2.00 kcal mol^{-1}, respectively. The calculated transition states for **1′**, **9′**, and **11′** are higher in Gibbs free energy than those of **1**, **9**, and **11** and are not competitive (see Supporting Information). However, **10** is more stable than **10′** by only 0.62 kcal mol^{-1}, and therefore both **10′** and **10** can compete in the addition reaction, as discussed below. Similar results were also found by Robiette et al.[27] As experimental studies and theoretical computation have shown complete *endo* selectivity in the AAD reaction,[10,13,14] we examined the diastereoselectivity of the pos-

sible *endo*-selective products. Nevertheless, for comparison, the corresponding *exo*-selective alternative has also been calculated.

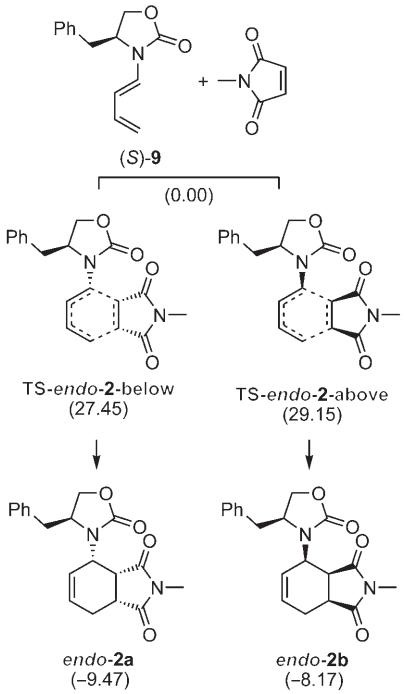
Scheme 9 shows the calculated final relative Gibbs free energies for the *endo* addition with the formation of the two diastereomeric products *endo*-**3a** and *endo*-**3b**, and their transition states are TS-*endo*-**3**-below and TS-*endo*-**3**-above, respectively. It is clear that both the transition state TS-*endo*-**3**-below and the product *endo*-**3a** are lower in Gibbs free energy than the corresponding TS-*endo*-**3**-above and *endo*-**3b** by 3.69 and 4.12 kcal mol^{-1}, respectively. This indicates that *endo*-**3a** is favored both kinetically and thermodynamically. Considering that TS-*endo*-**3**-below and TS-*endo*-**3**-above with a difference of 3.69 kcal mol^{-1} can compete, the expected ratio of the two diastereomers *endo*-**3a**/*endo*-**3b** should be 99:1, and the expected diastereoselectivity should be 98% *de*. This reproduces the experimentally obtained *de* values well (90% *de* by NMR spectroscopic measurement, Table 2) and shows a good agreement between theory and experiment.



Scheme 9. Calculated final relative Gibbs free energies (kcal mol^{-1}) of the possible products and transition states (TS) for the *endo*- and *exo*-cycloaddition of dienamide **1** to *N*-methylmaleimide.

The final Gibbs free energies of the corresponding *exo* addition are also summarized in Scheme 9. The two possible diastereomers are *exo*-**3a** and *exo*-**3b**, and the respective transition states are TS-*exo*-**3**-above and TS-*exo*-**3**-below, respectively. Between the two more-favored additions, the *endo*-addition transition states have lower barriers than the *exo*-addition transition states by about 6 kcal mol^{-1} (TS-*endo*-**3**-below vs. TS-*exo*-**3**-below), and the corresponding products are close in energy (*endo*-**3a** and *exo*-**3b**). This reveals that the *endo* addition is favored kinetically, whereas the *exo* addition is not competitive. This is in agreement with previous theoretical and experimental studies,[10,13,14,27] and therefore we will not pay further attention to the *exo* addition of other substituted 1,3-butadienes.

Further to **1**, we have also calculated the benzyl-substituted oxazolidinone derivative (*S*)-3-(buta-1,3-dienyl)-4-benzyloxazolidin-2-one (**9**). As already discussed, benzyl substitution is less diastereoselective than phenyl substitution, and it is therefore interesting to understand the origin of their difference. Scheme 10 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**, and their transition states are TS-*endo*-**2**-below and TS-*endo*-**2**-above, respectively.



Scheme 10. Calculated final relative Gibbs free energies (kcal mol^{-1}) of the possible products and transition states (TS) for the *endo*-cycloaddition of dienamide **9** to *N*-methylmaleimide.

As shown in Scheme 10, both the transition state TS-*endo*-**2**-below and the corresponding product *endo*-**2a** are lower in energy than TS-*endo*-**2**-above and product *endo*-**2b**,

indicating that the diastereoselectivity is favored kinetically and thermodynamically. However, these energy differences are smaller than those in Scheme 9, and this reveals that benzyl substitution results in lower diastereoselectivity than phenyl substitution. Indeed, the final Gibbs free energy difference between the two transition states of 1.70 kcal mol^{-1} gives a diastereoselectivity of 79% *de*, which is much lower than that of the phenyl-substituted diene (expected 98% *de*). Most importantly, this lower diastereoselectivity agrees also with our experimental finding (75% *de* by NMR spectroscopic measurement).

The observed energy difference can be explained by the geometrical difference between the two transition states TS-*endo*-**3**-above and TS-*endo*-**3**-below in Figure 3. In TS-*endo*-**3**-above, both the phenyl group and the dienophile are on the same side of the 1,3-butadiene moiety, whereas they are on opposite sides in TS-*endo*-**3**-below. In both cases the phenyl group adopts a nearly perpendicular orientation to the dienamide backbone. Similar findings have already been reported by Thornton and co-workers with 1,3-butadienyl esters.[34] Apart from the distances involved in C–C bond formation, the shortest nonbond distance is also very interesting. In TS-*endo*-**3**-above the shortest nonbond distance between the oxygen atom of the dienophile and the hydrogen atom of the phenyl ring is 2.216 Å. In TS-*endo*-**3**-below, the shortest nonbond distance between the oxygen atom of the dienophile and the hydrogen atom of the stereogenic center of the oxazolidinone ring is 2.493 Å. This makes it likely that the energy difference between TS-*endo*-**3**-above and TS-*endo*-**3**-below is of steric rather than electronic origin.

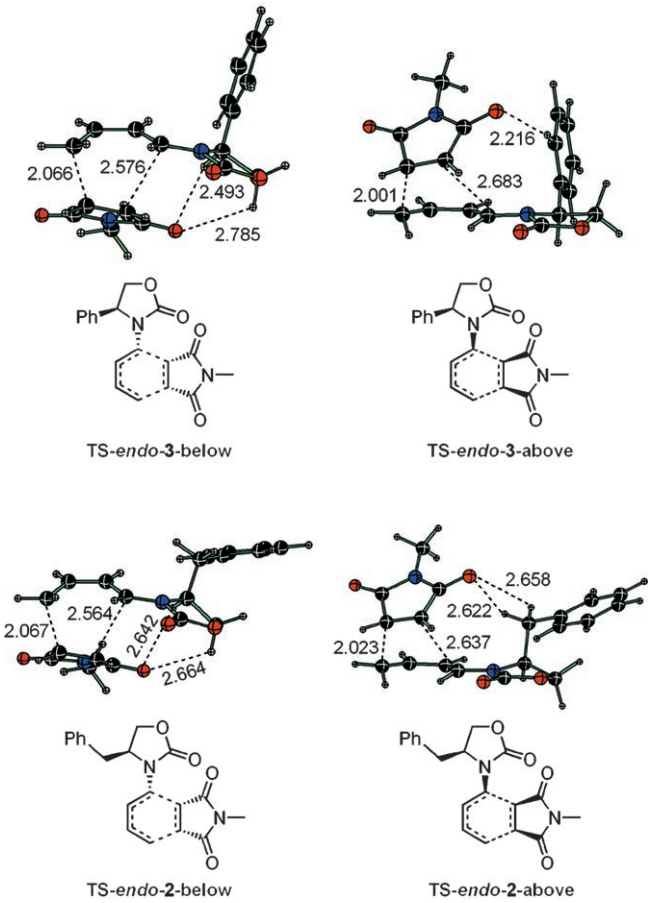


Figure 3. B3LYP/6–31G* optimized transition states for the formation of **2** and **3**.

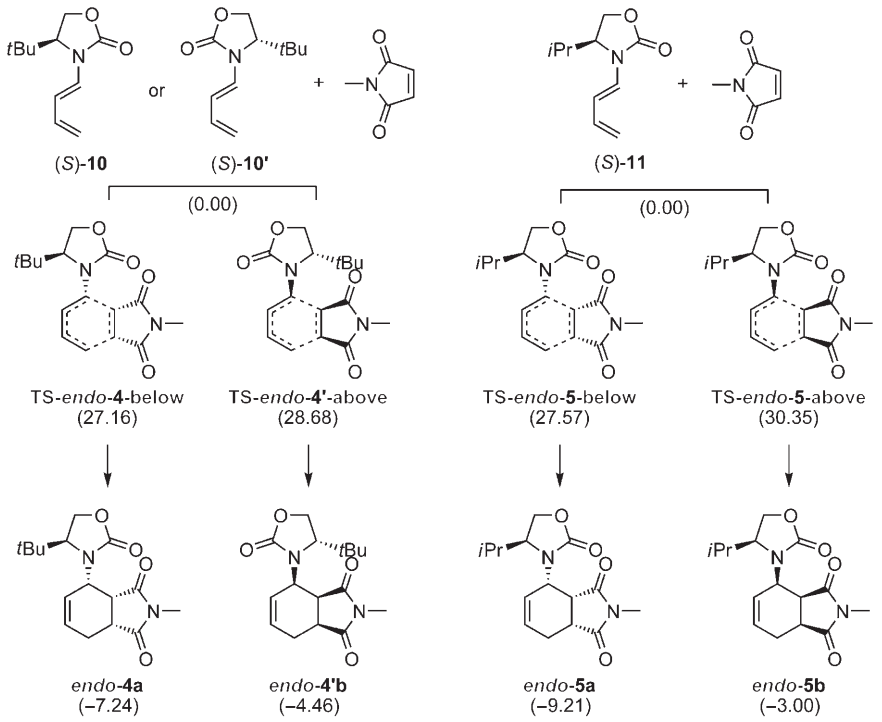
Similar behavior was found for the benzyl-substituted transition states TS-*endo*-**2**-above and TS-*endo*-**2**-below shown in Figure 3. In TS-*endo*-**2**-above the benzyl group and dienophile are on the same side, whereas they are on opposite sides in TS-*endo*-**2**-below. The nonbond distances in TS-*endo*-**2**-above are slightly shorter than in TS-*endo*-**2**-below, and these weaker differences are responsible for the smaller difference in energy barrier and result in lower diastereoselectivity. Direct comparison of TS-*endo*-**3**-above and TS-*endo*-**2**-above shows the stronger steric effect in the former than in the latter case, as indicated by the significant difference in the nonbond distances (2.216 Å vs. 2.622 Å/2.658 Å). This reveals the origin of the difference in the degree of the observed diastereoselectivities.

Apart from the difference between phenyl and benzyl substitution, we were interested in understanding the performance of *tert*-butyl and isopropyl substitution at the stereogenic center. Scheme 11 shows the calculated final relative Gibbs free energies for the *endo* cycloaddition of (*S*)-3-(buta-1,3-dienyl)-4-*tert*-butyloxazolidin-2-one (**10**) and (*S*)-3-(buta-1,3-dienyl)-4-isopropyloxazolidin-2-one (**11**) to *N*-methylmaleimide.

Notably, **10′** is only 0.61 kcal mol^{-1} higher in energy, and therefore both isomers can compete in the Diels–Alder reaction. Indeed, TS-*endo*-**4′**-above is more stable than TS-*endo*-**4**-above by 2.84 kcal mol^{-1} in Gibbs free energy, and the corresponding product *endo*-**4′b** is more stable than *endo*-**4b** by 4.69 kcal mol^{-1} in Gibbs free energy (see Supporting Information). These energy differences demonstrate the steric effect between the *tert*-butyl group and the 1,3-butadiene moiety in the starting materials, transition states, and products.

As shown in Scheme 11, however, TS-*endo*-**4**-below is lower in energy than TS-*endo*-**4′**-above by 1.52 kcal mol^{-1}, and *endo*-**4a** is more stable than *endo*-**4′b** by 2.78 kcal mol^{-1}. This indicates that the diastereoselectivity of *endo*-**4a** is favored both kinetically and thermodynamically. However, the small energy difference between the two transition states of 1.52 kcal mol^{-1} gives a diastereoselectivity of 74% *de*. This is also in perfect agreement with the value of 75% *de* obtained experimentally by NMR spectroscopic measurement (Table 2).

In contrast to the *tert*-butyl substituent of the *N*-dienyl lactams **10** and **10′**, the isopropyl residue exhibits the same energy effect as the phenyl and benzyl substituents. As shown in Scheme 11, *endo*-**5a** is favored both kinetically and thermodynamically by 2.78 kcal mol^{-1} and 6.21 kcal mol^{-1} in Gibbs free energy, respectively, and the expected diastereo-



Scheme 11. Calculated final relative Gibbs free energies (kcal mol^{-1}) of the products and transition states (TS) for the *endo*-cycloadditions of dienamides **10**, **10′**, and **11** to *N*-methylmaleimide.

selectivity is 94% *de*. Again, this agrees well with the experimental value (85% *de* by NMR spectroscopy).

This energy difference can also be explained by the geometrical difference between the two transition states TS-*endo*-**4′**-above and TS-*endo*-**4**-below, as well as TS-*endo*-**5**-above and TS-*endo*-**5**-below in Figure 4.

The *tert*-butyl group and dienophile moiety are on opposite sides in both the transitions states TS-*endo*-**4′**-above and TS-*endo*-**4**-below. Therefore no large energy effect can be expected, and this is associated with the lower diastereoselectivity. However, it is notable that the two forming C–C distances in TS-*endo*-**4**-below (2.044 Å and 2.608 Å) are shorter than those in TS-*endo*-**4′**-above (2.046 Å and 2.760 Å), indicating the stronger interaction and also the higher stability.

In contrast to that, both the isopropyl substituent and the dienophile in TS-*endo*-**5**-above, are on the same side of the 1,3-butadiene moiety, whereas they are on opposite sides in TS-*endo*-**5**-below. This steric effect should be mainly responsible for the energy difference, and therefore the diastereoselectivity.

Conclusions

In conclusion, the highly diastereoselective variant of our AAD reaction constitutes the most simple and direct high-yielding approach to asymmetric amido-functionalized cyclohexene derivatives (up to 94% yield and 90% *de*). The multicomponent methodology definitely circumvents the circuitous preparation of chiral *N*-dienyl lactams by in situ generation and subsequent trapping with dienophiles. Optimized reaction conditions were applied to different chiral amides, and the phenyl-substituted oxazolidinone showed the highest facial selectivity of the butadiene intermediate throughout the Diels–Alder step. Furthermore, DFT calculations confirmed that the *endo* addition in the cycloaddition step is kinetically more favored than the *exo* addition, whereas diastereoselectivity is due to both kinetic and thermodynamic control. It turned out that the selectivity of different-

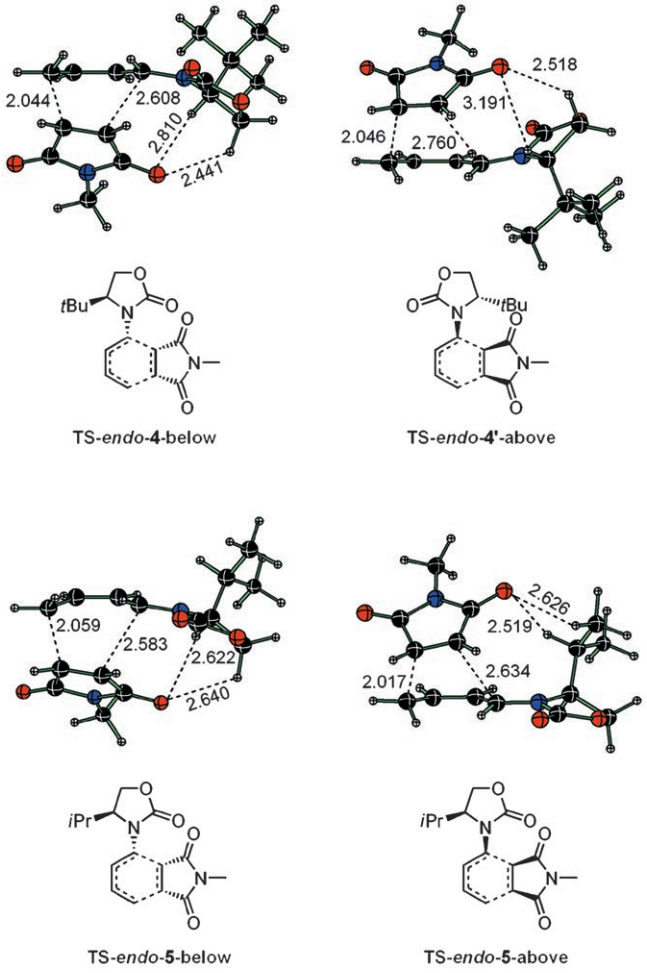


Figure 4. B3LYP/6–31G* optimized transition states for the formation of **4** and **5**.

ly substituted amido dienes is mainly caused by geometrical differences in the transition states. With regard to practicability it is interesting to note that the ubiquitous, off-shelf starting materials readily react even without special exclusion of air or water.[35]

Experimental Section

Computational Details

Due to the large number of substituted 1,4-butadienes and the corresponding transition states as well as the addition products, the computational work was carried out in several steps. All calculations were performed with the Gaussian 03 program package.[36] The frequency calculations at the ab initio HF/6–31G* and/or B3LYP density functional levels of theory characterize the optimized structures as energy-minimum structures without imaginary frequencies (NImag = 0), only real frequencies, and the transition states have only one imaginary frequency (NImag = 1).[37] For the phenyl-substituted oxazolidinone derivative, (*S*)-3-(1,3-buta-dienyl)-4-phenyloxazolidin-2-one (**1**), we carried out geometry optimizations and frequency calculations at both the ab initio HF/6–31G* and B3LYP/6–31G* density functional levels of theory for all possible reactants, transition states, and products. 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 for analyzing the selectivity. The final Gibbs energies are the sum of 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 at a temperature of 110 °C, the selectivity was estimated approximately at 400 K based on the relationship of $\Delta\Delta G^{\ddagger} = -RT\ln K$, in which $\Delta\Delta G^{\ddagger}$ is the difference in the Gibbs free activation energy, and K represents the considered equilibrium constant of the two competing transition states. The single C–N bond between 1,4-butadiene and oxazolidin-2-one can rotate easily, hence there are two isomers **1** and **1′**. However, we present only the reactions of the more-stable structure **1**, and those of the less-stable 1,4-butadiene are summarized in the Supporting Information. For general discussion and comparison, we calculated the *endo*/*exo* selectivity of **1** and *N*-methylmaleimide and the diastereoselectivity of the more-favored *endo*-selective addition. For all other substituted 1,4-butadienes, all possible reactants, transition structures, and products were calculated at the ab initio HF/6–31G* level for geometry optimizations and frequency calculations. These geometries were further refined at the B3LYP/6–31G* level, but the corresponding frequency calculations to obtain the thermal corrections to the final Gibbs free energies were only carried on the more-stable structures. On the basis of the favored *endo* selectivity for **1**, we focused only on the *endo* addition of the more-stable isomers of other substituted 1,4-butadienes. The final Gibbs free energies and the diastereoselectivity were obtained as mentioned above. As suggested by one reviewer, we also calculated the basis set superposition error (BSSE) of the two transition states, TS-*endo*-**3**-below and TS-*endo*-**3**-above at the B3LYP/6–311+G* level. The BSSE difference between these two transition states is about 0.04 kcal mol^{-1}, and this rather small value does not affect the calculated diastereoselectivity.

General

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 (Cambridge Instruments) and are uncorrected. IR spectra of solids were recorded as nujol mulls with KBr plates or KBr pellets on a Nicolet Magna 550, liquids were analyzed neat. Mass spectra were obtained on an AMD 402/3 from AMD Intectra (EI, 70 eV). HPLC analyses were performed on an HP 1100 equipped with a Luna C8 column by Phenomenex and a DAD detector. NMR spectra were recorded on Bruker AV 500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) and AV 400 (^{1}H: 400 MHz; ^{13}C: 100 MHz) spectrometers. The spectra were calibrated with respect to solvent signals ($CDCl_3$: δ (^{1}H) = 7.25 ppm, δ (^{13}C) = 77.0 ppm). The NMR signals were assigned by DEPT and 2D ^{1}H,^{1}H-COSY, and ^{1}H,^{13}C correlation spectra (HSQC, HMBC, and HETCOR). ^{1}H,^{1}H-NOESY spectra were recorded to determine the stereochemistry of compounds **2** and **3**.

Crystallographic Analysis

The crystallographic data of **2b** were collected with a STOE-IPDS diffractometer using graphite-monochromated $Mo_{K\alpha}$ radiation. The structures were solved by direct methods[38] and refined by full-matrix least-squares techniques[39] against F^2. Schakal was used for structural representations. Crystal data for **2b**: space group $P2_12_12_1$, orthorhombic, a = 5.911(1), b = 10.866(2), c = 26.654(5) Å, β = 90°, V = 1712.0(5) Å^3, Z = 4, ρ_{calcd} = 1.321 g cm^{-3}, 7588 reflections measured, 2216 were independent of symmetry, of which 1808 were observed ($I > 2\sigma(I)$), $R1$ = 0.0319, wR^2 (all data) = 0.069, 226 parameters. CCDC-634300 (**2b**) contains 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

2–8: Crotonaldehyde (4.50 mmol, 315 mg) was placed in a threaded pressure tube, and toluene (12 mL), amide (3 mmol), *N*-methylmaleimide (4.50 mmol, 500 mg), and *p*-toluene sulfonic acid monohydrate (2.00 mol %, 12.0 mg, 0.06 mmol) were then added. The reaction mixture was stirred at 110 °C for 24 h. After cooling, all volatile compounds were removed under reduced pressure. Silica-gel flash chromatography afforded the corresponding products.

Sample Preparation To Determine the Diastereoselectivity

The chiral amide (0.5 mmol) was placed in a 5-mL Wheaton reaction vial, and toluene (2 mL), aldehyde (0.75 mmol), dienophile (0.75 mmol), and *p*-toluene sulfonic acid monohydrate (2.0 mol %, 2.0 mg) were then 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 deuterated solvent (1 mL) and subjected to NMR spectroscopic analysis.

The NMR signals were assigned according to the numbering given in Figure 2.

2: 4-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-2-methyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione, 89 % yield, 75 % *de* (^{13}C IG NMR). Diastereomer **2a**: R_f = 0.14 (SiO_2, *n*-heptane/EtOAc = 1:1); m.p.: 52–54 °C; IR (nujol): $\tilde{\nu}$ = 3447 (w), 3059 (w), 3026 (w), 1749 (s), 1696 (s), 1288 (m), 1240 (w), 1123 (w), 1074 (w), 1030 (w), 1004 (m), 970 (vw), 911 (vw), 851 (vw), 830 (w), 766 (m), 728 (m), 701 (m), 671 (w), 566 (w), 504 cm^{-1} (w); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.20 (ddq*, $^2J_{7\text{-Hax},7\text{-Heq}}$ = 16.0 Hz, $^3J_{7\text{-Hax},7a\text{-H}}$ = 8.0 Hz, $^4J_{7\text{-Hax},5\text{-H}}$ = 3.0 Hz, $^3J_{7\text{-Hax},6\text{-H}}$ = 3.0 Hz, $^5J_{7\text{-Hax},4\text{-H}}$ = 3.0 Hz, 1H of 7-H$_{ax}$), 2.82 (ddd, $^2J_{7\text{-Heq},7\text{-Hax}}$ = 16.0 Hz, $^3J_{7\text{-Heq},6\text{-H}}$ = 6.9 Hz, $^3J_{7\text{-Heq},7a\text{-H}}$ = 1.9 Hz, 1H; 7-H$_{eq}$), 2.89 (dd, ^2J = 13.8 Hz, ^3J = 9.8 Hz, 1H of CH_2), 2.92 (s, 3H; 8-H), 3.11–3.17 (m, 2H; 1H each of 7a-H and CH_2), 3.66 (dd, $^3J_{3a\text{-H},7a\text{-H}}$ = 9.1 Hz, $^3J_{3a\text{-H},4\text{-H}}$ = 7.0 Hz, 1H; 3a-H), 4.12–4.18 (m, 2H; 1H each of 11″-H and 12-H), 4.39 (t*, ^3J = 8.2 Hz, ^2J = 8.2 Hz, 1H of 11′-H), 4.49 (m, 1H; 4-H), 6.04 (m, 1H; 6-H), 6.14 (dt*, $^3J_{5\text{-H},6\text{-H}}$ = 9.8 Hz, $^3J_{5\text{-H},4\text{-H}}$ = 3.2 Hz, $^4J_{5\text{-H},7\text{-H}ax}$ = 3.2 Hz, 1H; H-5), 7.18 (m, 2H; *o*-Ph), 7.25 (m, 1H; *p*-Ph), 7.32 ppm (m, 2H; *m*-Ph); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 23.7 (C7), 25.0 (C8), 38.5 (C7a), 40.5 (CH_2), 42.1 (C3a), 50.1 (C4), 56.8 (C12), 67.8 (C11), 126.2 (C5), 127.3 (*p*-Ph), 129.0 (CH_{arom}), 129.2 (CH_{arom}), 129.4 (C6), 135.7 (*i*-Ph), 157.9 (C9), 177.0 (CO), 179.1 ppm (CO); MS (EI, 70 eV): *m*/*z* (%) = 340 (1) $[M]^+$, 249 (48), 164 (100), 91 (28) $[C_7H_7]^+$, 86 (15), 79 (74), 77 (19) $[C_6H_5]^+$, 65 (10), 58 (12), no further peaks > 10 %; HRMS (EI, 70 eV): calcd for $C_{19}H_{20}N_2O_4$: 340.1423 $[M]^+$; found: 340.1423. Diastereomer **2b**: R_f = 0.09 (SiO_2, *n*-heptane/EtOAc = 1:1); m.p.: 147–148 °C; IR (nujol): $\tilde{\nu}$ = 3440 (w), 3061 (m), 3028 (m), 1746 (vs), 1696 (vs), 1602 (w), 1493 (m), 1353 (m), 1335 (m), 1317 (m), 1285 (m), 1249 (m), 1218 (m), 1202 (m), 1180 (w), 1165 (w), 1134 (m), 1095 (m), 1070 (m), 1056 (w), 1029 (w), 997 (s), 968 (w), 927

(w), 908 (w), 860 (w), 826 (m), 771 (m), 752 (s), 719 (m), 700 (s), 677 (m), 668 (w), 637 (w), 598 (m), 584 (m), 519 (m), 493 (m), 449 cm^{-1} (m); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.03$ (m, 1H; 7-H_{ax}), 2.81 (dd, $^2J = 13.9$ Hz, $^3J = 7.9$ Hz, 1H of CH_2), 2.88 (ddd, $^2J_{7\text{-Heq},7\text{-Hax}} = 16.4$ Hz, $^3J_{7\text{-Heq},6\text{-H}} = 6.9$ Hz, $^3J_{7\text{-Heq},7a\text{-H}} = 2.5$ Hz, 1H; 7-H_{eq}), 2.92 (s, 3H; 8-H), 3.03–3.08 (m, 2H; 1H each of 7a-H and CH_2), 3.32 (t*, $^3J_{3a\text{-H},7a\text{-H}} = 9.1$ Hz, $^3J_{3a\text{-H},4\text{-H}} = 9.1$ Hz, 1H; 3a-H), 3.98–4.03 (m, 2H; 1H each of 4-H and 11″-H), 4.31–4.36 (m, 1H; 12-H), 4.37 (t*, $^3J = 8.0$ Hz, $^2J = 8.0$ Hz, 1H; 11′-H), 5.97 (m, 1H; 6-H), 6.18 (dt*, $^3J_{5\text{-H},6\text{-H}} = 12.9$ Hz, $^3J_{5\text{-H},4\text{-H}} = 3.0$ Hz, $^4J_{5\text{-H},7\text{-Hax}} = 3.0$ Hz, 1H; 5-H), 7.18 (m, 2H; *o*-Ph), 7.26 (m, 1H; *p*-Ph), 7.32 ppm (m, 2H; *m*-Ph); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta = 21.8$ (C7), 25.1 (C8), 38.8 (C7a), 39.5 (CH_2), 40.7 (C3a), 48.8 (C4), 56.9 (C12), 67.4 (C11), 127.0 (C5), 127.3 (C6), 127.4 (*p*-Ph), 128.9 (CH_{arom}), 129.0 (CH_{arom}), 135.5 (*i*-Ph), 158.0 (C9), 176.4 (CO), 178.7 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 340 (1) $[M]^+$, 249 (73), 164 (30), 138 (19), 94 (12), 91 (38) $[C_7H_7]^+$, 86 (21), 79 (100), 77 (26) $[C_6H_5]^+$, 65 (13), 58 (16), no further peaks > 10%; HRMS (EI, 70 eV): calcd for $C_{19}H_{20}N_2O_4$: 340.1423 $[M]^+$; found: 340.1435.

3: 2-Methyl-4-((*S*)-2-oxo-4-phenyloxazolidin-3-yl)-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione, 94% yield, 90% *de* (^{13}C IG NMR). Diastereomer **3a**: $R_f = 0.11$ (SiO_2, *n*-heptane/EtOAc = 1:1); m.p.: 57–60 °C; IR (KBr): $\tilde{\nu} = 3448$ (m), 3061 (w), 3030 (w), 2955 (m), 2909 (w), 2856 (w), 1747 (vs), 1697 (vs), 1495 (m), 1437 (s), 1414 (s), 1385 (s), 1314 (m), 1288 (s), 1220 (m), 1126 (m), 1072 (m), 1040 (m), 1004 (m), 969 (w), 917 (w), 878 (w), 858 (w), 809 (w), 769 (m), 716 (s), 702 (s), 672 (m), 579 (m), 536 (w), 496 cm^{-1} (w); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.08$ (ddq*, $^2J_{7\text{-Hax},7\text{-Heq}} = 15.8$ 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, $^3J_{7\text{-Hax},4\text{-H}} = 3.0$ Hz, 1H; 7-H_{ax}), 2.73 (ddd, $^2J_{7\text{-Heq},7\text{-Hax}} = 15.8$ Hz, $^3J_{7\text{-Heq},6\text{-H}} = 7.2$ Hz, $^3J_{7\text{-Heq},7a\text{-H}} = 1.5$ Hz, 1H; 7-H_{eq}), 2.94 (s, 3H; 8-H), 3.13 (ddd, $^3J_{7a\text{-H},3a\text{-H}} = 9.0$ Hz, $^3J_{7a\text{-H},7\text{-Hax}} = 8.0$ Hz, $^3J_{7a\text{-H},7\text{-Heq}} = 1.5$ Hz, 1H; 7a-H), 3.66 (dd, $^3J_{3a\text{-H},7a\text{-H}} = 9.0$ Hz, $^3J_{3a\text{-H},4\text{-H}} = 7.0$ Hz, 1H; 3a-H), 4.12 (dd, $^2J = 8.2$ Hz, $^3J = 3.0$ Hz, 1H; 11″-H), 4.57 (m, 1H; 4-H), 4.85 (t*, $^2J = 8.2$ Hz, $^3J = 7.5$ Hz, 1H; 11′-H), 5.00 (dd, $^3J = 7.5$, 3.0 Hz, 1H; 12-H), 5.62 (dt*, $^3J_{5\text{-H},6\text{-H}} = 9.8$ Hz, $^3J_{5\text{-H},4\text{-H}} = 3.0$ Hz, $^4J_{5\text{-H},7\text{-Hax}} = 3.3$ Hz, 1H; 5-H), 5.75 (m, 1H; 6-H), 7.29 (m, 2H; *o*-Ph), 7.33 (m, 1H; *p*-Ph), 7.39 ppm (m, 2H; *m*-Ph); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta = 23.7$ (C7), 25.0 (C8), 38.3 (C7a), 41.8 (C3a), 50.4 (C4), 59.5 (C12), 71.6 (C11), 125.8 (*o*-Ph), 126.0 (C5), 128.6 (C6), 128.6 (*p*-Ph), 129.5 (*m*-Ph), 141.3 (*i*-Ph), 158.3 (C9), 177.5 (CO), 179.1 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 327 (1) $[M+H]^+$, 282 (20), 215 (24), 170 (24), 162 (100), 156 (14), 120 (15), 104 (82), 91 (27), 77 (34) $[C_6H_5]^+$, 68 (13), 53 (20), no further peaks > 10%; HR-MS (EI, 70 eV): calcd for $C_{18}H_{18}N_2O_4$: 326.1267 $[M]^+$; found: 326.1264. Diastereomer **3b**: $R_f = 0.08$ (SiO_2, *n*-heptane/EtOAc = 1:1); m.p.: 158–160 °C; IR (KBr): $\tilde{\nu} = 3452$ (m), 3050 (w), 2960 (m), 2924 (m), 2847 (m), 1732 (vs), 1701 (vs), 1481 (m), 1457 (m), 1437 (s), 1386 (m), 1340 (m), 1312 (m), 1287 (m), 1237 (m), 1180 (m), 1127 (s), 1093 (m), 1075 (m), 1041 (m), 1008 (m), 957 (w), 938 (m), 917 (m), 873 (w), 842 (m), 758 (m), 699 (s), 672 (m), 624 (w), 607 (w), 567 (m), 551 (w), 508 (m), 465 (m), 425 cm^{-1} (w); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.97$ (ddq*, $^2J_{7\text{-Hax},7\text{-Heq}} = 16.2$ Hz, $^3J_{7\text{-Hax},7a\text{-H}} = 6.9$ Hz, $^4J_{7\text{-Hax},5\text{-H}} = 3.0$ Hz, $^3J_{7\text{-Hax},6\text{-H}} = 3.0$ Hz, $^5J_{7\text{-Hax},4\text{-H}} = 3.0$ Hz, 1H; 7-H_{ax}), 2.83 (ddd, $^2J_{7\text{-Heq},7\text{-Hax}} = 16.2$ Hz, $^3J_{7\text{-Heq},6\text{-H}} = 6.8$ Hz, $^3J_{7\text{-Heq},7a\text{-H}} = 2.5$ Hz, 1H; 7-H_{eq}), 2.96 (s, 3H; 8-H), 3.04 (ddd, $^3J_{7a\text{-H},3a\text{-H}} = 9.2$ Hz, $^3J_{7a\text{-H},7\text{-Hax}} = 6.9$ Hz, $^3J_{7a\text{-H},7\text{-Heq}} = 2.5$ Hz, 1H; 7a-H), 3.29 (t*, $^3J_{3a\text{-H},7a\text{-H}} = 9.2$ Hz, $^3J_{3a\text{-H},4\text{-H}} = 9.2$ Hz, 1H; 3a-H), 3.69 (dq*, $^3J_{4\text{-H},3a\text{-H}} = 9.2$ Hz, $^3J_{4\text{-H},5\text{-H}} = 3.0$ Hz, $^4J_{4\text{-H},6\text{-H}} = 3.0$ Hz, $^5J_{4\text{-H},7\text{-Hax}} = 3.0$ Hz, 1H; 4-H), 4.07 (m, 1H; 11″-H), 4.73 (t*, $^3J = 8.8$ Hz, $^2J = 8.8$ Hz, 1H; 11′-H), 5.22 (t*, $^3J = 8.8$ Hz, $^2J = 8.8$ Hz, 1H; 12-H), 5.92 (m, 1H; 6-H), 6.17 (dt*, $^3J_{5\text{-H},6\text{-H}} = 10.0$ Hz, $^3J_{5\text{-H},4\text{-H}} = 3.0$ Hz, $^4J_{5\text{-H},7\text{-Hax}} = 3.0$ Hz, 1H; 5-H), 7.37 (m, 2H; *o*-Ph), 7.40–7.45 ppm (m, 3H; *m*-, *p*-Ph); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta = 21.7$ (C7), 25.2 (C8), 38.8 (C7a), 40.3 (C3a), 48.0 (C4), 61.1 (C12), 70.2 (C11), 127.2 (*o*-Ph), 126.9 (CH), 127.3 (CH), 129.4 (*p*-Ph), 129.6 (*m*-Ph), 137.3 (*i*-Ph), 157.9 (C9), 176.7 (CO), 178.7 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 327 (2) $[M+H]^+$, 282 (17), 215 (12), 170 (20), 162 (100), 156 (12), 120 (13), 104 (50), 91 (20), 77 (19) $[C_6H_5]^+$, 68 (6), 53 (10), no further peaks > 10%; HRMS (ESI): calcd for $C_{18}H_{19}N_2O_4$: 327.1345 $[M+H]^+$; found: 327.1350.

4: 4-((*S*)-4-*tert*-Butyl-2-oxooxazolidin-3-yl)-2-methyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione, 87% yield, 75% *de* (^1H NMR). Diastereomer **4a**: $R_f = 0.11$ (SiO_2, *n*-heptane/EtOAc = 1:1); m.p.: 184 °C; IR (nujol): $\tilde{\nu} = 3453$ (w), 3015 (w), 1734 (vs), 1697 (vs), 1488 (w), 1322 (w), 1306 (w), 1277 (m), 1224 (m), 1201 (m), 1156 (w), 1093 (m), 1075 (m), 1032 (w), 980 (w), 939 (w), 878 (w), 849 (w), 805 (m), 777 (m), 731 (w), 671 (w), 568 cm^{-1} (w); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.04$ (s, 9H of CH_3), 2.18 (m, 1H; 7-H_{ax}), 2.82 (m, 1H; 7-H_{eq}), 2.93 (s, 3H; 8-H), 3.11 (m, 1H; 7a-H), 3.53 (dd, $^2J = 8.5$ Hz, $^3J = 3.3$ Hz, 1H; 11″-H), 3.74 (t*, $^3J_{3a\text{-H},7a\text{-H}} = 8.9$ Hz, $^3J_{3a\text{-H},4\text{-H}} = 8.9$ Hz, 1H; 3a-H), 4.19–4.24 (m, 2H; 1H each of 4-H and 12-H), 4.39 (t*, $^3J = 8.5$ Hz, $^2J = 8.5$ Hz, 1H; 11′-H), 5.93 (m, 1H; 5-H), 5.97–6.03 ppm (m, 1H; 6-H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 22.7$ (C7), 25.0 (C8), 25.8 (CH_3), 35.5 (C_{quat}), 38.9 (C7a), 41.4 (C3a), 51.6 (C4), 65.5 (C12), 65.9 (C11), 127.1 (C5), 128.9 (C6), 159.3 (C9), 176.6 (CO), 179.1 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 307 (1) $[M+H]^+$, 249 (43) $[M-C_4H_9]^+$, 164 (100), 86 (18), 79 (92), 77 (23), 57 (13), 41 (21), 29 (11), no further peaks > 10%; HRMS (EI, 70 eV): calcd for $C_{16}H_{22}N_2O_4$: 306.1580 $[M]^+$; found: 306.1573. Diastereomer **4b**: $R_f = 0.07$ (SiO_2, *n*-heptane/EtOAc = 1:1); m.p.: 255 °C; IR (nujol): $\tilde{\nu} = 3437$ (w), 3015 (w), 1748 (vs), 1695 (vs), 1338 (w), 1314 (m), 1290 (m), 1237 (m), 1207 (m), 1171 (m), 1133 (m), 1098 (m), 1054 (m), 1030 (w), 1005 (m), 997 (m), 975 (m), 955 (w), 853 (w), 839 (m), 818 (w), 758 (m), 737 (w), 705 (m), 674 (w), 581 cm^{-1} (w); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.97$ (s, 9H of CH_3), 2.10 (m, 1H; 7-H_{ax}), 2.90 (m, 1H; 7-H_{eq}), 2.94 (s, 3H; 8-H), 3.09 (m, 1H; 7a-H), 3.34 (t*, $^3J_{3a\text{-H},7a\text{-H}} = 9.2$ Hz, $^3J_{3a\text{-H},4\text{-H}} = 9.2$ Hz, 1H; 3a-H), 3.59 (dd, $^2J = 8.5$ Hz, $^3J = 3.2$ Hz, 1H; 11″-H), 4.14–4.19 (m, 2H; 1H each of 4-H and 12-H), 4.51 (t*, $^3J = 8.5$ Hz, $^2J = 8.5$ Hz, 1H; 11′-H), 5.97 (m, 1H; 6-H), 6.25 ppm (dt*, $^3J_{5\text{-H},6\text{-H}} = 10.0$ Hz, $^3J_{5\text{-H},4\text{-H}} = 3.1$ Hz, $^4J_{5\text{-H},7\text{-Hax}} = 3.1$ Hz, 1H; 5-H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 21.7$ (C7), 25.2 (C8), 25.7 (CH_3), 35.3 (C_{quat}), 39.0 (C7a), 41.2 (C3a), 51.2 (C4), 64.3 (C12), 65.3 (C11), 127.1 (C6), 127.7 (C5), 159.0 (C9), 176.7 (CO), 178.7 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 306 (1) $[M]^+$, 249 (48) $[M-C_4H_9]^+$, 164 (80), 142 (20), 138 (14), 94 (10), 86 (20), 79 (100), 77 (25), 67 (10), 57 (15), 41 (25), 29 (11), no further peaks > 10%; HRMS (EI, 70 eV): calcd for $C_{16}H_{22}N_2O_4$: 306.1580 $[M]^+$; found: 306.1578.

5: 4-((*S*)-4-Isopropyl-2-oxooxazolidin-3-yl)-2-methyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione, 92% yield, 85% *de* (^1H NMR). Diastereomer **5a**: $R_f = 0.10$ (SiO_2, *n*-heptane/EtOAc = 1:1); m.p.: 133 °C; IR (nujol): $\tilde{\nu} = 3442$ (w), 3045 (m), 3015 (m), 2724 (w), 1743 (vs), 1695 (vs), 1483 (m), 1411 (m), 1342 (m), 1312 (m), 1284 (m), 1247 (m), 1226 (m), 1212 (m), 1199 (m), 1172 (m), 1130 (m), 1119 (m), 1106 (w), 1086 (m), 1051 (m), 1009 (m), 993 (m), 978 (m), 968 (m), 914 (w), 880 (w), 829 (m), 800 (m), 768 (m), 752 (m), 735 (m), 723 (m), 706 (m), 670 (m), 639 (m), 610 (w), 594 (m), 558 (m), 509 (w), 455 (m), 440 cm^{-1} (w); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.91$ (d, $^3J = 6.9$ Hz, 3H; CH_3), 0.97 (d, $^3J = 6.7$ Hz, 3H; CH_3), 2.06 (m, 1H; CH), 2.13–2.21 (m, 1H; 7-H_{ax}), 2.79 (m, 1H; 7-H_{eq}), 2.91 (s, 3H; 8-H), 3.15 (m, 1H; 7a-H), 3.80 (dd, $^3J_{3a\text{-H},7a\text{-H}} = 9.0$ Hz, $^3J_{3a\text{-H},4\text{-H}} = 6.8$ Hz, 1H; 3a-H), 3.85 (dt*, $^3J_{12\text{-H},11'\text{-H}} = 8.5$ Hz, $^3J_{12\text{-H},11''\text{-H}} = 2.5$ Hz, $^3J_{12\text{-H},CHMe2} = 2.5$ Hz, 1H; 12-H), 4.22 (dd, $^2J = 8.5$ Hz, $^3J = 2.5$ Hz, 1H; 11″-H), 4.44–4.49 (m, 2H; 1H each of 4-H and 11′-H), 5.97–6.02 (m, 1H; 6-H), 6.06 ppm (dt*, $^3J_{5\text{-H},6\text{-H}} = 9.9$ Hz, $^3J_{5\text{-H},4\text{-H}} = 3.0$ Hz, $^4J_{5\text{-H},7\text{-Hax}} = 3.0$ Hz, 1H; 5-H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta = 14.3$ (CH_3), 18.3 (CH_3), 23.9 (C7), 24.9 (C8), 31.0 (CH), 38.5 (C7a), 41.6 (C3a), 50.4 (C4), 60.0 (C12), 64.0 (C11), 126.3 (C5), 129.2 (C6), 158.5 (C9), 177.1 (CO), 179.2 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 292 (1) $[M]^+$, 249 (22) $[M-C_3H_7]^+$, 233 (10), 181 (16), 164 (74), 138 (20), 128 (16), 94 (17), 86 (21), 79 (100), 77 (28), 67 (12), 58 (17), 41 (20), 39 (10), no further peaks > 10%; HRMS (EI, 70 eV): calcd for $C_{15}H_{20}N_2O_4$: 292.1423 $[M]^+$; found: 292.1416. Diastereomer **5b**: $R_f = 0.06$ (SiO_2, *n*-heptane/EtOAc = 1:1); m.p.: 163–166 °C; IR (KBr): $\tilde{\nu} = 3441$ (m), 3057 (w), 2959 (m), 2929 (m), 2876 (m), 1749 (vs), 1697 (vs), 1487 (m), 1437 (s), 1387 (s), 1337 (m), 1309 (m), 1289 (m), 1242 (m), 1206 (m), 1176 (m), 1131 (m), 1102 (m), 1055 (m), 1001 (m), 982 (w), 968 (w), 914 (w), 874 (w), 842 (m), 817 (w), 759 (m), 726 (w), 705 (m), 696 (m), 672 (m), 633 (w), 584 (m), 507 (w), 460 cm^{-1} (w); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.91$ (d, $^3J = 6.7$ Hz, 3H; CH_3), 0.93 (d, $^3J = 7.0$ Hz, 3H; CH_3), 2.03–2.14 (m, 2H; 1H each of 7-H_{ax} and CH), 2.91 (m, 1H; 7-H_{eq}), 2.94 (s, 3H; 8-H), 3.10 (ddd, $^3J_{7a\text{-H},3a\text{-H}} = 9.0$ Hz, $^3J_{7a\text{-H},7\text{-Hax}} = 6.9$ Hz, $^3J_{7a\text{-H},7\text{-Heq}} = 2.7$ Hz, 1H; 7a-H), 3.33 (t*, $^3J_{3a\text{-H},7a\text{-H}} = 9.0$ Hz, $^3J_{3a\text{-H},4\text{-H}} = 9.0$ Hz, 1H; 3a-H), 3.95 (m, 1H; 4-H), 4.01–4.08 (m, 2H; 1H each of 11″-H and 12-H), 4.38 (t*, $^3J = 8.0$ Hz, $^2J = 8.0$ Hz, 1H; 11′-H), 5.95–6.00 (m, 1H; 6-H), 6.18 ppm (dt*, $^3J_{5\text{-H},6\text{-H}} =$

9.9 Hz, $^3J_{5\text{-H},4\text{-H}}=3.0$ Hz, $^4J_{5\text{-H},7\text{-Hax}}=3.0$ Hz, 1H; 5-H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta=14.4$ (CH_3), 17.7 (CH_3), 21.8 (C7), 25.2 (C8), 28.0 (CH), 38.8 (C7a), 40.7 (C3a), 47.9 (C4), 60.1 (C12), 63.1 (C11), 127.2 (CH), 127.3 (CH), 158.2 (C9), 176.5 (CO), 178.7 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 292 (1) $[M]^+$, 249 (15) $[M-C_3H_7]^+$, 233 (17), 181 (21), 164 (100), 138 (28), 128 (33), 94 (28), 86 (24), 79 (86), 77 (26), 67 (12), 58 (18), 41 (21), 39 (10), 28 (39), no further peaks > 10%; HRMS (ESI): calcd for $C_{15}H_{21}N_2O_4$: 293.1502 $[M+H]^+$; found: 293.1501.

6: 4-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-2-methyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione, 92% yield, 75% *de* (^1H NMR). Diastereomer **6a**: $R_f=0.14$ (SiO_2, *n*-heptane/EtOAc = 1:1); ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.20$ (m, 1H; 7-H_{ax}), 2.80–2.91 (m, 2H; 1H each of CH_2 and 7-H_{eq}), 2.92 (s, 3H; 8-H), 3.11–3.17 (m, 2H; 1H each of CH_2 and 7a-H), 3.66 (dd, $^3J_{3a\text{-H},7a\text{-H}}=9.1$ Hz, $^3J_{3a\text{-H},4\text{-H}}=7.0$ Hz, 1H; 3a-H), 4.12–4.18 (m, 2H; 1H each of 12-H and 11-H), 4.39 (t*, $^3J=8.2$ Hz, $^2J=8.2$ Hz, 1H of 11-H), 4.49 (m, 1H; 4-H), 6.04 (m, 1H; 6-H), 6.14 (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), 7.18 (m, 2H of CH_{arom}), 7.25 (m, 1H of CH_{arom}), 7.32 ppm (m, 2H of CH_{arom}); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta=23.7$ (C7), 25.0 (C8), 38.5 (C7a), 40.5 (CH_2), 42.1 (C3a), 50.1 (C4), 56.8 (C12), 67.8 (C11), 126.2 (C5), 127.3 (CH_{arom}), 129.0 (CH_{arom}) 129.2 (CH_{arom}), 129.4 (C6), 135.7 (C_{arom}), 157.9 (C9), 177.0 (CO) 179.1 ppm (CO). Diastereomer **6b**: $R_f=0.09$ (SiO_2, *n*-heptane/EtOAc = 1:1); ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.03$ (m, 1H of 7-H), 2.80–2.90 (m, 2H; 1H each of CH_2 and 7-H), 2.92 (s, 3H; 8-H), 3.03–3.08 (m, 2H; 1H each of 7a-H and CH_2), 3.32 (t*, $^3J_{3a\text{-H},7a\text{-H}}=9.1$ Hz, $^3J_{3a\text{-H},4\text{-H}}=9.1$ Hz, 1H; 3a-H), 3.98–4.03 (m, 2H; 1H each of 4-H and 11-H), 4.31–4.38 (m, 2H; 1H each of 12-H and 11-H), 5.97 (m, 1H; 6-H), 6.18 (dt*, $^3J_{5\text{-H},6\text{-H}}=12.9$ Hz, $^3J_{4\text{-H},5\text{-H}}=3.0$ Hz, $^4J_{5\text{-H},7\text{-Hax}}=3.0$ Hz, 1H; 5-H), 7.18 (m, 2H of CH_{arom}), 7.26–7.32 ppm (m, 3H of CH_{arom}); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta=21.8$ (C7), 25.1 (C8), 38.8 (C7a), 39.5 (CH_2), 40.7 (C3a), 48.7 (C4), 56.9 (C12), 67.4 (C11), 127.0 (C5), 127.3 (C6), 127.4 (CH_{arom}), 128.9 (CH_{arom}), 129.0 (CH_{arom}), 135.5 (C_{arom}), 158.0 (C9), 176.4 (CO), 178.7 ppm (CO).

7: (*S*)-Methyl-1-(2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-5-oxopyrrolidine-2-carboxylate, 77% yield, 74% *de* (^{13}C IG NMR). Diastereomer **7a**: $R_f=0.17$ (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); ^1H NMR (500 MHz, $CDCl_3$): $\delta=2.08$ (m, 1H; 1H of CH_2), 2.16 (qq*, $^2J_{7\text{-Hax},7\text{-Heq}}=15.8$ Hz, $^3J_{7a\text{-H},7\text{-Hax}}=8.0$ Hz, $^4J_{5\text{-H},7\text{-Hax}}=3.3$ Hz, $^3J_{6\text{-H},7\text{-Hax}}=3.0$ 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, $^2J_{7\text{-Hax},7\text{-Heq}}=15.8$ Hz, $^3J_{6\text{-H},7\text{-Heq}}=7.2$ Hz, $^3J_{7a\text{-H},7\text{-Heq}}=1.6$ Hz, 1H; 7-H_{eq}), 2.88 (s, 3H; 8-H), 3.15 (ddd, $^3J_{3a\text{-H},7a\text{-H}}=9.0$ 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; CH_3), 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, $^3J_{4\text{-H},5\text{-H}}=3.0$ Hz, 1H; 5-H), 5.92 ppm (m, 1H; 6-H); $^{13}C\{^1H\}$ 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 (CH_3), 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): calcd for $C_{15}H_{18}N_2O_5$: 306.1216 $[M]^+$; found: 306.1208. Diastereomer **7b**: $R_f=0.09$ (SiO_2, *n*-heptane/EtoAc = 1:5). NMR data are extracted from a spectrum of a mixture of **7a** and **7b**; not all signals are given owing to overlapping with signals of the major diastereomer **7a**. ^1H NMR (500 MHz, $CDCl_3$): $\delta=2.88$ (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; CH_3), 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); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta=22.2$ (CH_2), 23.7 (CH_2), 24.9 (C8), 30.0 (CH_2), 39.0 (C7a), 41.6 (C3a), 49.4 (C4), 52.5 (CH_3), 61.3 (C12), 126.7 (C6), 127.4 (C5), 172.9 (CO), 175.9 (CO), 177.1 (CO), 179.0 ppm (CO).

8: 4-((*S*)-2-(Hydroxymethyl)-5-oxopyrrolidin-1-yl)-2-methyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione, 84% yield, < 15% *de* (HPLC). Diastereomer **8a**: $R_f=0.10$ (SiO_2, CH_3Cl/MeOH = 40:1); m.p.: 164 °C; IR (KBr): $\tilde{\nu}=3398$ (m), 3052 (w), 3037 (w), 2935 (m), 2909 (m), 2847 (m), 1776 (m), 1696 (vs), 1659 (vs), 1439 (s), 1384 (m), 1361 (m), 1273 (m), 1214 (m), 1164 (w), 1139 (w), 1123 (m), 1089 (m), 1060 (m), 1008 (m), 977 (w), 961 (w), 937 (w), 891 (w), 869 (w), 850 (w), 803 (m), 756 (w), 738 (w), 695 (w), 667 (m), 626 (w), 587 (w), 565 (w), 508 (w), 488 (w), 465 (w), 442 cm^{-1} (w); ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.15$–2.33 (m, 4H; 7-H_{ax} and 3H of CH_2), 2.64–2.73 (m, 1H of CH_2), 2.84 (m, 1H; 7-H_{eq}), 2.91 (s, 3H; 8-H), 3.17 (m, 1H; 7a-H), 3.48–3.64 (m, 3H; 2H of CH_2 and 1H of OH), 3.96–4.00 (m, 1H; 12-OH), 4.04 (dd, $^3J_{3a\text{-H},7a\text{-H}}=8.8$ Hz, $^3J_{3a\text{-H},4\text{-H}}=7.2$ Hz, 1H; 3a-H), 4.47 (m, 1H; 4-H), 5.95–6.01 (m, 1H; 6-H), 6.08 ppm (dt*, $^3J_{5\text{-H},6\text{-H}}=9.8$ Hz, $^4J_{5\text{-H},7\text{-Hax}}=3.3$ Hz, $^3J_{5\text{-H},4\text{-H}}=3.3$ Hz, 1H; 5-H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta=22.3$ (CH_2), 23.5 (C7), 25.0 (C8), 31.2 (CH_2), 39.2 (C7a), 41.5 (C3a), 50.9 (C4), 59.8 (C12), 64.5 (CH_2), 126.3 (C5), 128.3 (C6), 177.8 (CO), 178.7 (CO), 179.1 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 278 (3) $[M]^+$, 247 (38), 136 (26), 116 (16), 84 (100), 79 (34), 41 (10), 28 (19), no further peaks > 10%; HRMS (EI, 70 eV): calcd for $C_{14}H_{18}N_2O_4$: 278.1267 $[M]^+$; found: 278.1270. Diastereomer **8b**: $R_f=0.15$ (SiO_2, CH_3Cl/MeOH = 40:1); IR (neat):$\tilde{\nu}=3402$ (s), 3051 (w), 2950 (s), 1772 (s), 1699 (vs), 1444 (s), 1386 (s), 1287 (s), 1180 (m), 1126 (m), 1083 (m), 1051 (m), 1007 (m), 952 (w), 916 (w), 893 (w), 858 (w), 821 (m), 807 (m), 782 (w), 748 (m), 703 (m), 653 (m), 572 (m), 515 (m), 473 cm^{-1} (w); ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.15$–2.26 (m, 4H; 7-H_{ax} and 3H of CH_2), 2.52–2.59 (m, 1H of CH_2), 2.88 (m, 1H; 7-H_{eq}), 2.94 (s, 3H; 8-H), 3.09–3.15 (m, 1H; 7a-H), 3.29 (t*, $^3J_{3a\text{-H},7a\text{-H}}=9.4$ Hz, $^3J_{3a\text{-H},4\text{-H}}=9.4$ Hz, 1H; 3a-H), 3.59–3.65 (m, 1H of CH_2), 3.69–3.72 (m, 1H; 12-H), 3.98 (m, 1H of CH_2), 4.04 (m, 1H; 4-H), 4.67 (br d, $^3J=10.5$ Hz, 1H; OH), 5.87 (dt*, $^3J_{5\text{-H},6\text{-H}}=9.9$ Hz, $^4J_{5\text{-H},7\text{-H}ax}=2.8$ Hz, $^3J_{5\text{-H},4\text{-H}}=2.8$ Hz, 1H; H-5), 5.95–6.01 ppm (m, 1H; 6-H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta=21.7$ (C7), 21.8 (CH_2), 25.3 (C8), 31.1 (CH_2), 39.5 (C7a), 42.9 (C3a), 48.8 (C4), 63.0 (C12), 64.2 (CH_2), 127.4 (C5), 127.4 (C6), 176.3 (CO), 178.9 (CO), 178.9 ppm (CO); MS (EI, 70 eV): *m/z* (%) = 278 (1) $[M]^+$, 247 (28), 136 (37), 84 (100), 79 (33), 55 (11), 41 (12), no further peaks > 10%; HRMS (EI, 70 eV): calcd for $C_{14}H_{18}N_2O_4$: 278.1267 $[M]^+$; found: 278.1268.

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