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Stereoselective, Temperature-Dependent [2+2] Cycloaddition of *N*,*N*-Dialkylhydrazones to *N*-Benzyl-*N*-(benzyloxycarbonyl)aminoketene

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The Staudinger-like [2+2] cycloaddition of aliphatic hydrazones derived from (2*R*,5*R*)-1-amino-2,5-dimethylpyrrolidine to *N*-benzyl-*N*-(benzyloxycarbonyl)aminoketene takes place to afford the corresponding β-lactams in good yields when *i*Pr$_2$EtN is used as the base. The reaction proceeds in all cases with excellent stereocontrol to afford exclusively products having the (3*R*) configuration. Temperature was observed to exert a strong influence on the *cis*/*trans* selectivity, allowing in most cases the obtention of single *trans* or *cis* cycloadducts simply by performing the reactions at 80 °C or room temperature, respectively. Additional experiments support the hypothesis that the observed stereochemistry is the result of C=N isomerization in the zwitterionic intermediate, which takes place by a nucleophilic addition−rotation−elimination mechanism effected by the nucleophiles present in the reaction medium. Release of the dialkylamino group by oxidative cleavage of the N–N bond affords valuable compounds such as α,β-diamino acids and the azetidinone cores of monobactam antibiotics such as aztreonam and carumonam.

Introduction

β-Lactam antibiotics have been key drugs for over 70 years in man's fight against infectious diseases. They are the most widely employed type of antibacterial agents and, therefore, constitute one of the major cornerstones in medicinal chemistry.[1] The discovery[2] and structural elucidation of the first isolated members of this family of antibiotics (penicillin G[3] and cephalosporin C[4]) boosted the activity of synthetic chemists towards the development of methodologies for the stereoselective construction of the β-lactam skeleton.[5] Nowadays, the interest in these compounds is sustained because of the constant need for new drugs displaying broader antibacterial activity and/or different biological profiles to combat bacteria that have built up resistance against most traditional compounds. Additionally, the use of β-lactams for other purposes is attracting attention. For instance, recent reports have described the development of inhibitors such as serine protease,[6] human leukocyte elastase,[7] cytomegalovirus protease,[8] thrombin,[9] prostate specific antigen,[10] cholesterol absorption,[11] and tryptase.[12] Some β-lactams have also shown anticancer activity,[13] and recent studies by Palomo and co-workers have demonstrated the utility of synthetic β-lactams as the key structures in the synthesis of conformationally restricted peptidomimetics of biological significance.[14] Moreover, β-lactams can be considered as protected β-amino acids and have been used as chiral building blocks in synthetic organic chemistry.[15]

Within the large family of β-lactams, the 3-amino-substituted derivatives have a specific importance owing to their bioactivity. The discovery of monocyclic β-lactam antibiotics,[16] named and classified as monobactams, and the introduction of drugs such as aztreonam (Azactam®) and carumonam on the one hand, and the additional interest in 3-amino-β-lactams as valuable precursors to biologically active α,β-diamino acid derivatives[17] on the other, have stimulated considerable efforts towards the development of stereoselective routes to the key 3-aminoazetidin-2-one substructure.[18] Among the methods available for the stereocontrolled synthesis of the azetidinone skeleton and their open-chain β-amino acid analogues, the [2+2] ketene–imine cycloaddition,[19] known as the Staudinger reaction,[20] appears as one of the most widely used strategies due to its simplicity and the availability of the starting materials (Scheme 1).

One of the strategies used involves the cycloaddition of imines and ketenes substituted by an oxygenated functionality that is later used as the leaving group in the introduction of nitrogen nucleophiles. For instance, the cycloaddition of sulfonylketenes to chiral imines has been used for the stereoselective construction of 3-sulfonyl-β-lactams. Ensuing substitution by azide enabled the synthesis of bio-

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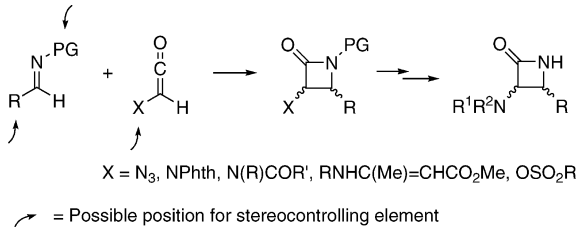


Scheme 1. The ketene–imine [2+2] cycloaddition approach to 3-amino-β-lactams.

logically important carbohydrates[21] and of the taxol amino side-chain.[22]

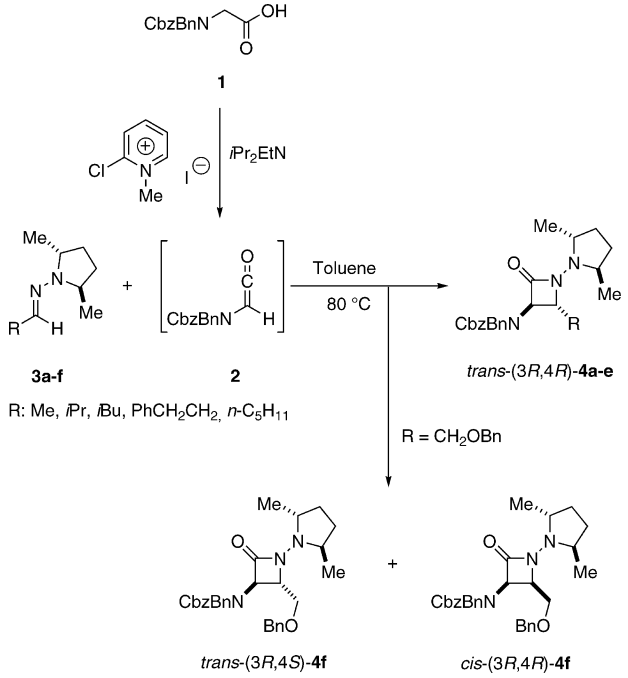
[2+2] cycloaddition to 3-azidoketenes followed by reduction of the azido group has also been used for the synthesis of 3-amino-β-lactams.[23] Another versatile method that affords enantiopure 3-amino-β-lactams and α,β-diamino acids makes use of the [2+2] cycloaddition of *N*-acyl-protected aminoketenes to imines, a reaction that has been accomplished by introducing chiral auxiliaries into the imine or ketene components.[24] Additionally, α-branched α-amino-β-lactams and peptides derived therefrom have been obtained by diastereoselective alkylation of 4-unsubstituted derivatives.[25]

These methodologies, however, in general suffer some limitations mainly imposed by the poor stability of the required imines. With very few exceptions,[26] enolizable, simple aliphatic aldimines cannot be used in this type of cycloaddition because of their low thermal stability and the competitive deprotonation by the base required for the in situ generation of the ketene. Based on our previous experiences with *N*,*N*-dialkylhydrazones,[27] we recently started a project based on the higher stability of these compounds relative to *N*-alkyl(aryl)imines in the Staudinger reaction. It was discovered that formaldehyde derivatives behave as a stable class of monomeric methanimines in their reaction with functionalized (alkoxy- and amino)ketenes[28] and that the stability of aliphatic *N*,*N*-dialkylhydrazones is key to the straightforward synthesis of 3-alkoxy-4-alkyl(aryl)azetidin-2-ones and that of the corresponding isoserines.[29]

We now wish to present the results of our study of the use of chiral, aliphatic *N*,*N*-dialkylhydrazones as imine surrogates in the Staudinger-like [2+2] cycloaddition to α-aminoketenes in the synthesis of 3-amino-4-alkylazetidin-2-ones[30] and α,β-diamino acids, and of the marked influence of the base and the reaction temperature on the course of the reaction.

Results and Discussion

The preliminary experiments were conducted using *N*-benzyl-*N*-(benzyloxycarbonyl)glycine (**1**) as the precursor to aminoketene **2** and 2-chloro-1-methylpyridinium iodide as the activating agent. This choice was made on the basis of previous results from the synthesis of 4-unsubstituted azetidin-2-ones[28] (Scheme 2). On the other hand, the C_2-symmetric (2*R*,5*R*)-2,5-dimethylpyrrolidine, identified in an optimization study of the cycloaddition of *N*,*N*-dialkylhydrazones to benzyloxyketene,[29] was used as the hydrazone chiral auxiliary assuming in principle that similar interactions should govern the stereochemical outcome of the reaction with the nitrogenated ketene **2**. Thus, aliphatic hydrazones **3a**–**e** were synthesized and allowed to react with **1** under the previously established conditions (toluene, 80 °C, Et_3N)[29b] to afford the corresponding cycloadducts **4a**–**e** as single diastereomers. Disappointingly, though, products **4** were obtained in low yields (25–50%) under these conditions. Therefore, different reaction parameters were screened to improve the chemical efficiency of the cycloaddition. From this study, a remarkable influence of the base used for the generation of the ketene was identified. Thus, when *i*Pr_2EtN was used as the base, the corresponding β-lactams **4a**–**e** were obtained in much better yields (59–74%, Table 1, entries 1–5), and again as single diastereomers. In sharp contrast, other bases tested (Bn_3N, proton sponge, di-*tert*-butylpyridine, etc.) gave no reaction under these conditions.



Scheme 2. Synthesis of 3-amino-4-alkylazetidin-2-ones **4**.

Anomalous behavior was observed in the reaction of benzyloxyacetaldehyde-derived hydrazone **3f** with **2**. Under the same conditions, the expected cycloadduct **4f** was also obtained in 66% yield, but in this case as a 54:46 *trans*/*cis* separable mixture of (3*R*,4*S*) and (3*R*,4*R*) diastereomers (Table 1, entry 6).

The unexpected *trans* selectivity observed in the formation of cycloadducts **4a**–**e** contrasts the excellent *cis* selectivity observed with the same auxiliary in the cycloaddition of hydrazones **3** with benzyloxyketene,[29] which suggests that a different mechanism operates in this case. A *cis*/*trans* base-catalyzed epimerization at C-3 was eventually pro-

Table 1. Synthesis of 4-alkyl-3-aminoazetidin-2-ones **4**.

Entry	Starting material	R	Product	% Yield[a]	$(3R)/(3S)_{trans}$[b]	*trans*/*cis*[b]	$(3R)/(3S)_{cis}$[b]
1	**3a**	Me	(3*R*,4*R*)-**4a**	74	>99:1	>99:1	–
2	**3b**	*i*Pr	(3*R*,4*R*)-**4b**	66	>99:1	>99:1	–
3	**3c**	*i*Bu	(3*R*,4*R*)-**4c**	70	>99:1	>99:1	–
4	**3d**	$PhCH_2CH_2$	(3*R*,4*R*)-**4d**	70	>99:1	>99:1	–
5	**3e**	*n*-C_5H_{11}	(3*R*,4*R*)-**4e**	59	>99:1	>99:1	–
6	**3f**	$BnOCH_2$	(3*R*,4*S*/*R*)-**4f**	66	>99:1	54:46[c]	>99:1
7	**3g**	*trans*-crotyl	(3*R*,4*S*)-**4g**	67	–	<1:99	>99:1

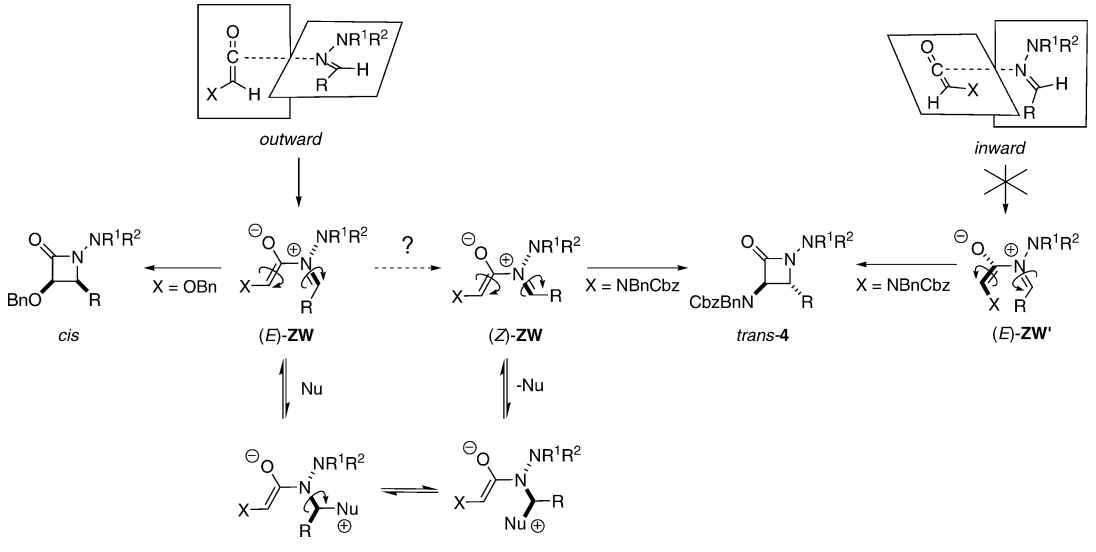
[a] Yield of isolated product **4**. Reactions were performed on a 1 mmol scale in toluene at 80 °C. [b] Determined by ^1H and ^{13}C NMR analysis of the crude reaction mixtures. [c] Separable by column chromatography.

posed to explain the anomalous *trans* selectivity observed. This possibility, however, was considered unconvincing because such an epimerization to the observed (3*R*,4*R*)-**4** requires the initial formation of the (3*S*,4*R*) isomer, that is, a product that holds the opposite configuration at C-3 with respect to that observed regularly in related systems of the used auxiliary. Moreover, unsuccessful attempts to epimerize available *cis* compounds ruled out this possibility,[31] confirming that kinetically controlled products are obtained under the reaction conditions. This is in agreement with previous reports on the absence of epimerization of related *cis*-β-lactams in the presence of triethylamine.[32]

The *trans* selectivity observed could alternatively be explained as being the result of an "inward" approach of the aminoketene to the hydrazone, leading to a zwitterionic intermediate (*E*)-**ZW′**, which, upon direct conrotatory ring-closure, leads to the observed (3*R*,4*S*) configuration (Scheme 3). However, previous studies have revealed that cycloaddition via "inward" intermediates is more energy-demanding than via the "outward" intermediates when electron-rich ketenes are involved.[33] Therefore, the observed stereochemistry and a comparison with the stereochemistry observed in the cycloaddition to benzyloxyketene [*cis* (3*R*,4*R*) products] suggest a consistent path (outward approach of the ketene) for the formation of the zwitterionic intermediates (*E*)-**ZW**. In the absence of severe steric interactions (X = OBn) the intermediate directly undergoes ring-closure to afford the *cis* product, but for hindered substrates this intermediate may also undergo C–N bond isomerization to the less hindered zwitterion (*Z*)-**ZW** and subsequent ring-closure to the observed *trans* β-lactam.[34]

The zwitterion (*E*)-**ZW** isomerization mechanism remains unknown, but there is evidence from the Staudinger reaction between ketenes and imines that is not consistent with a direct isomerization by C–N bond rotation.[35] On the other hand, a multi-step (*E*)-**ZW**/(*Z*)-**ZW** isomerization process initiated by attack of a nucleophile on the azomethine carbon of *E*-(**ZW**) followed by rotation of the resulting C–N single bond and finally elimination of the nucleophile to the *Z*-(**ZW**) intermediate seems to be a more plausible pathway.

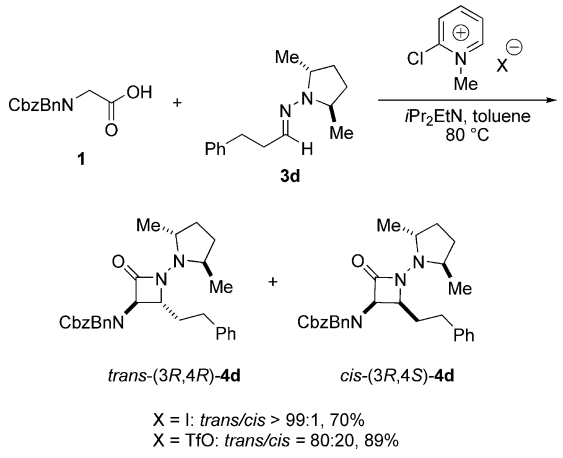
In addition to the above-mentioned steric effect, the different stereochemical outcomes for benzyloxy- and aminoketene **2** may also be partly affected by the experimental conditions. The benzyloxyketene is generated in situ by elimination of benzyloxyacetyl chloride in the presence of triethylamine, but the aminoketene derivative **2** is obtained by reaction of the corresponding α-amino acid precursor **1** and 2-chloro-1-methylpyridinium iodide in the presence of iPr_2EtN. It is clear that there is a marked difference in reaction conditions, such as the nature and concentration of the nucleophiles (Et_3N, iPr_2EtN, iodide, chloride). We propose



Scheme 3. Suggested model for the relative stereochemistry of the cycloaddition.

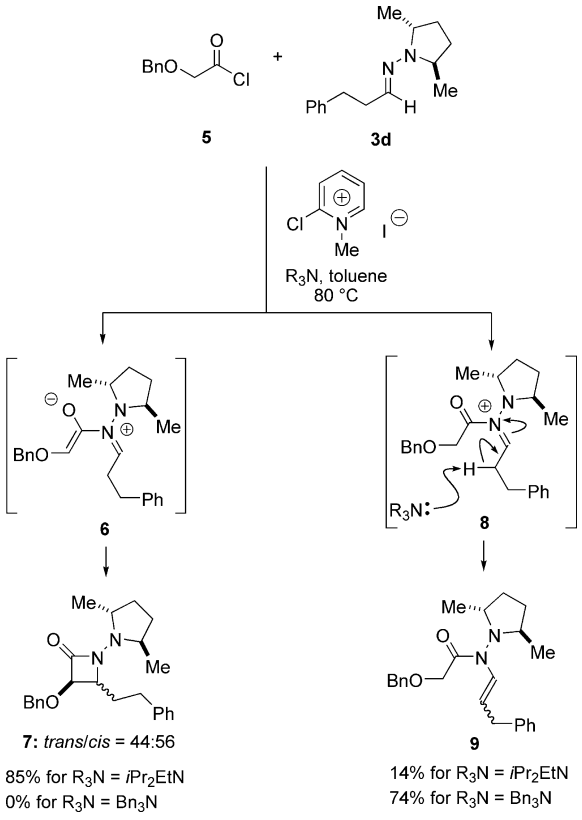
that the *trans* configuration observed when the aminoketene is generated from *N*-benzyl-*N*-(benzyloxycarbonyl)glycine is the result of two factors: a) The inhibition of the direct ring-closure of the (*E*)-**ZW** intermediate due to considerable steric interactions and b) a favored isomerization process assisted by the presence of suitable nucleophiles and the high temperatures applied.

Experiments were carried out in order to support this hypothesis. First, when 2-chloro-1-methylpyridinium triflate was used to generate the aminoketene **2**, the reaction with hydrazone **3d** (Scheme 4) afforded the corresponding β-lactam **4d** in an 80:20 *trans*/*cis* ratio, in sharp contrast to the exclusive formation of the *trans* isomer observed when the 2-chloro-1-methylpyridinium iodide was used as the activating agent. The decrease in the *trans*-β-lactam product is consistent with the use of triflate, a less nucleophilic anion than iodide. The substantial amount of *trans* product observed even in these conditions can be explained by the presence of the chloride anion (also able to behave as a nucleophile),[36] liberated in the activation of *N*-benzyl-*N*-(benzyloxycarbonyl)glycine (**1**) by 2-chloro-1-methylpyridinium triflate in the presence of *i*Pr_2EtN.



Scheme 4. Effect of nucleophiles on the *trans*/*cis* ratio of the cycloaddition.

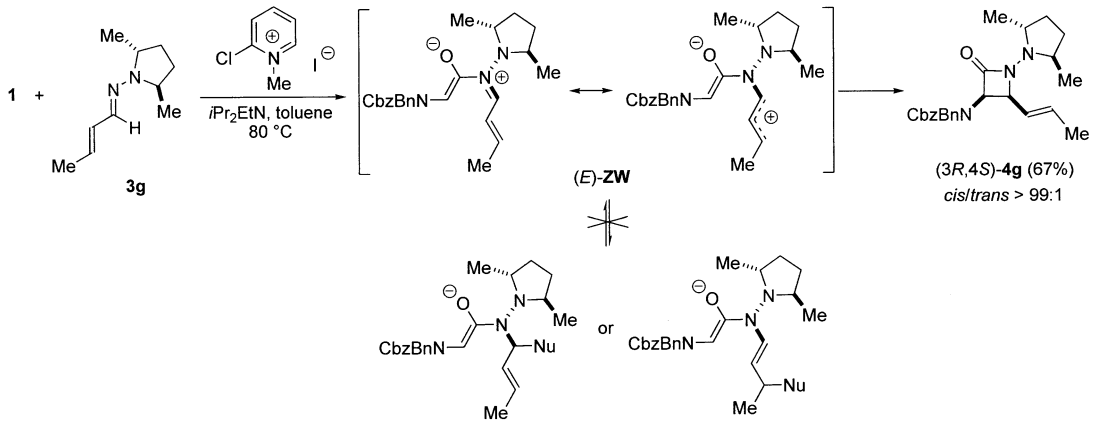
We next investigated the reaction of benzyloxyacetyl chloride **5** with hydrazone **3d** (Scheme 5). The reaction was performed using the same conditions as those applied in the experiments with the aminoketene precursor **1** (12 equiv. of *i*Pr_2EtN, 6.5 equiv. of 2-chloro-1-methylpyridinium iodide, dry toluene, 80 °C). Under these conditions, the corresponding β-lactam **7** was obtained in 85% yield as a 44:56 *trans*/*cis* mixture, in contrast to the 9:91 *trans*/*cis* ratio observed under previously optimized conditions (dry toluene, 80 °C, 8 equiv. of Et_3N).[29] Again, the increase in the *trans*/*cis* β-lactam product ratio supports the hypothesis of a marked influence by nucleophiles (iodide anions introduced) on the stereoselectivity of the reaction. Note also the formation under these conditions of enamide **9** as a byproduct in 14% yield. The formation of this byproduct is interpreted as being the result of an acylation of the hydrazone **3d** by the acyl chloride **5** to form the corresponding acyliminium chloride **8**. This intermediate directly yields the observed byproduct **9** by hydrogen abstraction by bases, as illustrated in Scheme 5. Interestingly, an experiment carried out using Bn_3N instead of the more basic *i*Pr_2EtN and Et_3N afforded enamide **9** (92:8 mixture of isomers) as the sole reaction product in 74% yield; no traces of cycloaddition products were detected.



Scheme 5. Reaction of hydrazone **3d** with benzyloxyacetyl chloride **5**.

In order to help clarify the role of the base in the initial ketene formation step, the reactions of **5** with Et_3N, *i*Pr_2EtN, and Bn_3N were performed in C_6D_6 solution under argon and monitored by ^{1}H NMR spectroscopy. The formation of the ketene was complete at room temp. within 2 h in the Et_3N case, whereas unreacted **5** was observed with *i*Pr_2EtN, and the transformation was even slower with Bn_3N. We conclude that there is competition between ketene formation (favored by using *i*Pr_2EtN and Et_3N) and the acylation of hydrazone (favored by Bn_3N); the first pathway leads mainly to β-lactam products, whereas the second produces only enamide derivative **9**.

Finally, it was reasoned that any additional stabilization of the C=N bond in the initially formed (*E*)-**ZW** intermediate should slow down the addition of nucleophiles, thereby making the isomerization process more difficult. Although the synthetic interest in aromatic derivatives of **4** (R = Ar) is not so high due to the availability of suitable alternatives,[24] we decided to study the effect of stabilization of the C=N bond by its conjugation with an aromatic group in the zwitterionic intermediate, presuming that a higher amount of the *cis* product would be observed in these cases.

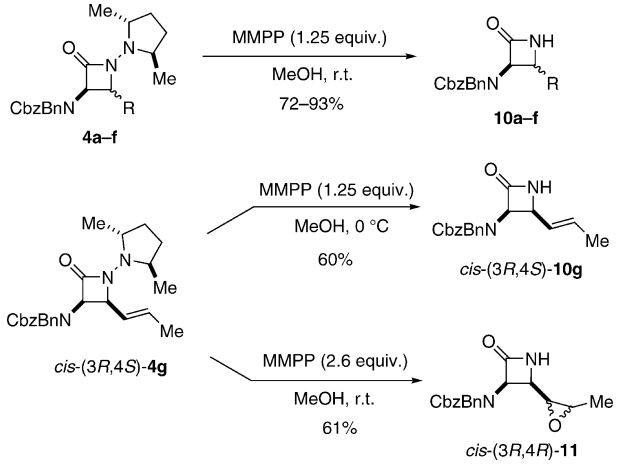


Scheme 6. Reaction of crotonaldehyde derivative **3g** with *N*-benzyl-*N*-(benzyloxycarbonyl)glycine (**1**).

Unfortunately, hydrazones **3** derived from benzaldehyde (R = Ph) or even *p*-methoxybenzaldehyde (R = *p*-$MeOC_6H_4$) were found to be unreactive; no cycloaddition product was formed under any of the conditions attempted. As an alternative, crotonaldehyde hydrazone **3g** was chosen as a model substrate to investigate the effect of stabilization by conjugation. Interestingly, the cycloaddition of this substrate proceeded to afford the expected product **4g** as a single *cis*-(3*R*,4*S*) isomer in 67% yield (Scheme 6, Table 1, entry 7). This result is consistent with the proposed nucleophile-assisted isomerization hypothesis, as it leads to the conclusion that the addition of nucleophiles to the corresponding (*E*)-**ZW** intermediate is inhibited, in this case by the additional stabilization of the allylic cation, thereby preventing the isomerization of the C=N bond.

Further investigations showed a marked influence of temperature on the stereoselectivity of the reaction.[37] When reactions of aminoketene **2** with hydrazones **3c**–**f** were conducted at room temperature the corresponding *cis*-(3*R*,4*S*)-**4c**–**e** and *cis*-(3*R*,4*R*)-**4f** compounds were obtained in moderate-to-good yields and with good-to-excellent *cis*/*trans* selectivities. Moreover, no cycloadducts having the (3*S*) configuration were detected (Table 2). The formation of small amounts of the *trans*-(3*R*,4*R*)-**4c**,**e** isomers were observed in some cases (entries 1 and 3), but a simple separation by flash chromatography allowed the isolation of the major *cis* isomers (3*R*,4*S*)-**4c** and (3*R*,4*S*)-**4e** in pure form. When hydrazone **3f** was used, the reaction at room temperature also led to the desired *cis* product (3*R*,4*R*)-**4f** in high yield (entry 4), but an optimum reaction temperature of 40 °C was established in this case, affording pure *cis*-(3*R*,4*R*)-**4f** in an excellent 95% yield (entry 5).

Release of the 2,5-dimethylpyrrolidine auxiliary was required to afford the target β-lactams. Taking into account the poor results observed when the known reduction procedures were applied to the required N–N bond cleavage in the related 3-(benzyloxy)azetidinones,[29] compounds **4a**–**g** were deprotected by applying the recently reported methodology for the oxidative deamination of hydrazides (Scheme 7).[38] Accordingly, treatment of compounds **4** with methanolic magnesium monoperoxyphthalate hexahydrate



Scheme 7. Release of the chiral auxiliary: oxidative cleavage of the N–N bond.

Table 2. Effect of temperature on the *trans*/*cis* ratio of the cycloaddition.

Entry	Starting material	R	*T* [°C]	*t*	Major product	% Yield[a]	*trans*/*cis*[b]	$(3R)/(3S)_{cis}$
1	**3c**	*i*Bu	r.t.	5 d	*cis*-(3*R*,4*S*)-**4c**	40	8:92 (<1: 99)[c]	>99:1
2	**3d**	$PhCH_2CH_2$	r.t.	4 d	*cis*-(3*R*,4*S*)-**4d**	72	<1:99	>99:1
3	**3e**	*n*-C_5H_{11}	r.t.	4 d	*cis*-(3*R*,4*S*)-**4e**	41	13:87 (<1: 99)[c]	>99:1
4	**3f**	$BnOCH_2$	r.t.	4 d	*cis*-(3*R*,4*R*)-**4f**	81	<1:99	>99:1
5	**3f**	$BnOCH_2$	40	29 h	*cis*-(3*R*,4*R*)-**4f**	95	<1:99	>99:1

[a] Yield of isolated *cis* product. Reactions were performed on the 1 mmol scale in toluene. [b] Determined by ^1H and ^{13}C NMR analysis of the crude reaction mixtures. [c] Separable by column chromatography.

(MMPP·$6H_2O$) readily afforded *cis* or *trans* free β-lactams **10a**–**f** in high yields (72–93%) and in enantiomerically pure form (Table 3). The presence of the C=C double bond in **4g** made the selective *N*-oxidation of the amino nitrogen difficult. Nevertheless, the desired product **10g** could be obtained in 60% yield by performing the reaction at a lower temperature (0 °C). Under these conditions, epoxide **11** was obtained as a byproduct in 33% yield. This compound was obtained as the major product in 61% yield when an excess of 2.6 equiv. of MMPP was employed at room temperature.

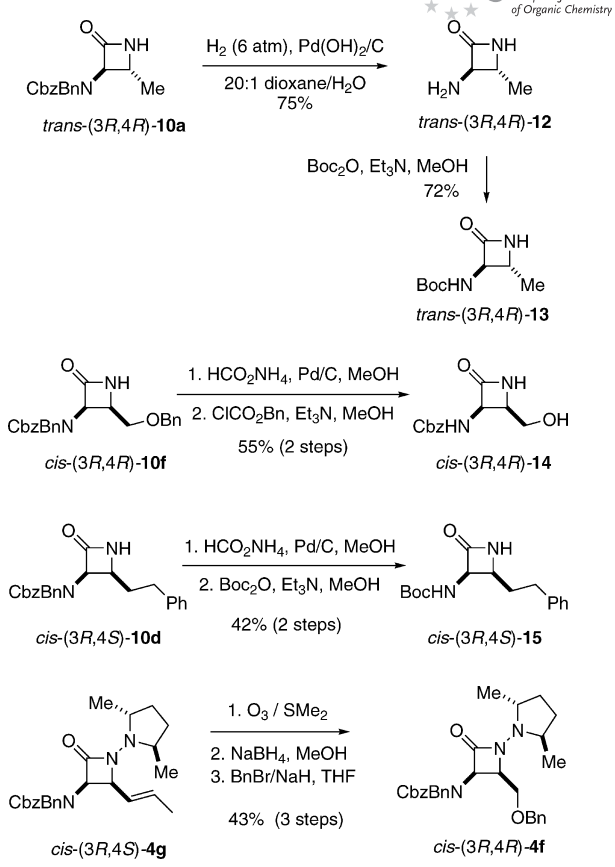
Table 3. Synthesis of the azetidin-2-ones **10a**–**g** by oxidative N–N bond cleavage of β-lactams **4a**–**g**.[a]

Starting material	R	Product	% Yield[b]
trans-(3*R*,4*R*)-**4a**	Me	*trans*-(3*R*,4*R*)-**10a**	90
trans-(3*R*,4*R*)-**4b**	*i*Pr	*trans*-(3*R*,4*R*)-**10b**	72
trans-(3*R*,4*R*)-**4c**	*i*Bu	*trans*-(3*R*,4*R*)-**10c**	85
cis-(3*R*,4*S*)-**4c**	*i*Bu	*cis*-(3*R*,4*S*)-**10c**	93
trans-(3*R*,4*R*)-**4d**	$PhCH_2CH_2$	*trans*-(3*R*,4*R*)-**10d**	73
cis-(3*R*,4*S*)-**4d**	$PhCH_2CH_2$	*cis*-(3*R*,4*S*)-**10d**	91
trans-(3*R*,4*R*)-**4e**	*n*-C_5H_{11}	*trans*-(3*R*,4*R*)-**10e**	74
cis-(3*R*,4*S*)-**4e**	*n*-C_5H_{11}	*cis*-(3*R*,4*S*)-**10e**	84
cis-(3*R*,4*R*)-**4f**	$BnOCH_2$	*cis*-(3*R*,4*R*)-**10f**	74
cis-(3*R*,4*S*)-**4g**	*trans*-crotyl	*cis*-(3*R*,4*S*)-**10g**	60[c]
cis-(3*R*,4*S*)-**4g**	*trans*-crotyl	*cis*-(3*R*,4*R*)-**11**	61[d]

[a] Reactions were performed in MeOH on the 1 mmol scale using 1.25 equiv. of MMPP at room temp., unless indicated otherwise. [b] Isolated yield. [c] The reaction was performed at 0 °C. [d] The reaction was performed with 2.6 equiv. of MMPP.

The absolute configuration of these compounds was assigned by chemical correlation with the transformations shown in Scheme 8. Compound *trans*-(3*R*,4*R*)-**10a** was transformed into the corresponding free amine **12** in 75% yield by hydrogenation with Pearlman's catalyst [$Pd(OH)_2$/C] in 20:1 dioxane/H_2O.[39] Ensuing protection using Boc_2O/Et_3N in MeOH led to the known *N*-Boc derivative **13** in 72% yield.[40] The absolute stereochemistry of the *cis* adduct (3*R*,4*R*)-**10f** was also assigned after chemical correlation. Transfer hydrogenation of *cis*-(3*R*,4*R*)-**10f** with HCO_2NH_4 and Pd/C followed by protection with $ClCO_2Bn$ were performed to afford the known *N*-Cbz derivative (3*R*,4*R*)-**14** in 55% overall yield.[41] Compound *cis*-(3*R*,4*S*)-**10d** was also transformed into the known *N*-Boc derivative **15**[42] in 42% overall yield by again using transfer hydrogenation with HCO_2NH_4 and Pd/C and ensuing protection by Boc_2O/Et_3N in MeOH. Finally, the absolute configuration of *cis*-(3*R*,4*S*)-**4g** was also assigned by chemical correlation. In this case, transformation into *cis*-(3*R*,4*R*)-**4f** was accomplished by ozonolysis of the C=C bond, reduction of the resulting aldehyde, and protection with benzyl bromide. The absolute configurations of all other compounds were assigned by analogy.

The products **10** are direct synthetic precursors of several bioactive compounds, including α,β-diamino acids and monobactams. For instance, compounds **13** and **14** are enantiomers of the key β-lactam components of the antibiotics aztreonam and carumonam, respectively (Figure 1). The availability of both enantiomers of the used auxiliary allows the obtention of products with the desired absolute



Scheme 8. Chemical correlations used for the determination of the absolute configurations.

configuration. Note, the acetaldehyde and benzyloxyacetaldehyde imine derivatives required for the above syntheses are particularly prone to enolization. This fact highlights the stabilizing properties of the dialkylamino group in primary aliphatic hydrazones.

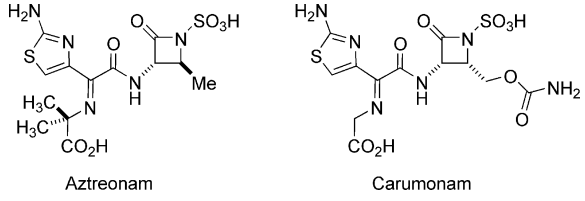
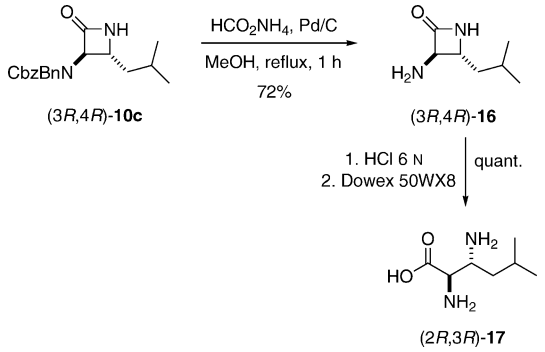


Figure 1. Antibiotics aztreonam and carumonam.

Finally, compounds **10** can also be considered as direct precursors to valuable α,β-diamino acids. As an illustrative example, standard transformations from compound (3*R*,4*R*)-**10c** were applied to the synthesis of the corresponding free diamino acid (2*R*,3*R*)-**17**, which was obtained in good overall yield (Scheme 9).

Conclusions

The multiple roles played by the dialkylamino group of hydrazones **3** are key to the successful synthesis of target 3-amino-β-lactams. First, the n→π conjugation of the N lone-pair with the C=N bond stabilizes these compounds, in par-



Scheme 9. Synthesis of α,β-diamino acid (2*R*,3*R*)-**17**.

ticular against the otherwise favored enolization to enehydrazine tautomers. Secondly, the 2,5-dimethylpyrrolidine moiety efficiently controls the approach of the hydrazone to the aminoketene **2**, always very selectively leading to products with the (3*R*) configuration. Thirdly, the dialkylamino chiral auxiliary simultaneously behaves as a protecting group that can be efficiently released under mild conditions to afford the target 3-amino-β-lactams. These properties, combined with the tunable, temperature-controlled *cis*/*trans* selectivity results in a short and versatile route to α-amino-β-lactams **10**, which can be obtained with the desired absolute and relative configurations. In particular, the a priori unexpected *trans* selectivity observed at high temperatures can be considered as a particularly valuable circumstance from the synthetic point of view as the available methods for the stereocontrolled ketene–aliphatic imine cycloaddition lead to *cis* cycloadducts. Finally, the synthetic value of this methodology is demonstrated by the synthesis of α,β-diamino acid **17** and those of compounds **13** and **14**, the β-lactam cores of monobactam antibiotics such as aztreonam and carumonam.

Experimental Section

General Methods: Toluene was distilled from sodium benzophenone ketyl and CH_2Cl_2 from CaH_2 immediately prior use; Et_3N from Na and *i*Pr_2EtN from KOH. All other reagents and solvents were purified by standard procedures or were used as obtained from commercial sources as appropriate. Aqueous solutions were all saturated, unless otherwise stated. Flash column chromatography was carried out using silica gel (Merck, 0.063–0.200 mm or 0.040–0.063 mm) or prepacked silica columns (FLASH biotage). ^{1}H NMR spectra were recorded at 300 or 500 MHz and are reported as follows: δ values in ppm (multiplicity, coupling constant *J* in Hz, number of protons). Residual protic solvent was used as the internal reference. ^{13}C NMR spectra were recorded at 75 or 125 MHz. Chemical shifts are quoted in ppm and referenced to the appropriate solvent peak. Hydrazones **3b**–**d** were synthesized according to previously described procedures.[29b]

General Procedure for the Synthesis of Hydrazones 3a and 3e–g: Et_3N (3.5 mL, 25 mmol) was added to a solution of (2*S*,5*S*)-hexane-2,5-diol (1.2 g, 10 mmol) in dry CH_2Cl_2 (20 mL) under argon. The mixture was cooled to –30 °C and MsCl (2 mL, 25 mmol) was added dropwise. The reaction was stirred at 0 °C for 3 h and then 1 M HCl (20 mL) was added. The organic layer was washed with saturated $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. The resulting residue was cooled to 0 °C and hydrazine monohydrate (9.7 mL, 200 mmol) was added. The reaction was stirred at room temp. overnight and then saturated $NaHCO_3$ was added. The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and filtered. Na_2SO_4 and the corresponding aldehyde (1.2–1.5 equiv.) were added to the ethereal solution. The mixture was stirred until consumption of the starting material (1–3 d), then filtered and concentrated. The purification method, yields, and spectral and analytical data for compounds **3a** and **3e**–**g** are as follows.

(2*R*,5*R*)-1-(Ethylideneamino)-2,5-dimethylpyrrolidine (3a): From acetaldehyde (0.85 mL, 15 mmol), after 3 d purification by distillation (65 °C, 15–20 mbar), 300 mg (25% over three steps) of **3a** was obtained as a colorless liquid: $[\alpha]_D^{25} = -6.7$ (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.2 Hz, 6 H), 1.41–1.52 (m, 2 H), 1.92 (d, *J* = 5.1 Hz, 3 H), 2.04–2.17 (m, 2 H), 3.57–3.65 (m, 2 H), 6.68 (q, *J* = 5.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 19.1, 29.1, 55.1, 133.6 ppm. IR (film): ṽ = 2965, 2926, 2875, 1722, 1607, 1448, 1378, 1327, 1218, 1174, 1123 cm^{-1}. HRMS: calcd. for $C_8H_{15}N_2$ 139.1235; found 139.1231.

(2*R*,5*R*)-1-(Hexylideneamino)-2,5-dimethylpyrrolidine (3e): From hexanal (1.82 mL, 15 mmol), after 1 d flash chromatography (1:16 Et_2O/hexane), 1.32 g (67% over three steps) of **3e** was obtained as an oil: $[\alpha]_D^{25} = -16.3$ (*c* = 1.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H), 1.06 (d, *J* = 6.2 Hz, 6 H), 1.26–1.37 (m, 4 H), 1.39–1.53 (m, 4 H), 2.02–2.17 (m, 2 H), 2.18–2.25 (m, 2 H), 3.56–3.65 (m, 2 H), 6.62 (t, *J* = 5.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 17.8, 22.7, 27.8, 29.3, 31.6, 33.5, 55.3, 138.9 ppm. IR (film): ṽ = 2964, 2927, 2866, 1610, 1460, 1371, 1319, 1208, 1171 cm^{-1}. HRMS: calcd. for $C_{12}H_{23}N_2$ 195.1861; found 195.1868.

(2*R*,5*R*)-1-[2-(Benzyloxy)ethylideneamino]-2,5-dimethylpyrrolidine (3f): From benzyloxyacetaldehyde (1.74 mL, 12 mmol), after 3 d flash chromatography (1:20 → 1:8 Et_2O/hexane), 1.77 g (72%, over three steps) of **3f** was obtained as an oil: $[\alpha]_D^{22} = -42.8$ (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (d, *J* = 6.3 Hz, 6 H), 1.43–1.55 (m, 2 H), 2.05–2.19 (m, 2 H), 3.64–3.72 (m, 2 H), 4.12 (dd, *J* = 11.7, 5.4 Hz, 1 H), 4.17 (dd, *J* = 11.7, 5.4 Hz, 1 H), 4.53 (s, 2 H), 6.54 (t, *J* = 5.5 Hz, 1 H), 7.24–7.38 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1, 29.4, 55.2, 71.3, 71.9, 127.6, 128.1, 128.5, 128.7, 138.6 ppm. IR (film): ṽ = 3023, 2967, 2928, 2872, 1593, 1458, 1371, 1315, 1212, 1077, 846, 735, 703 cm^{-1}. HRMS: calcd. for $C_{15}H_{22}N_2O$ 246.1732; found 246.1736.

(2*R*,5*R*)-1-(But-2-enylideneamino)-2,5-dimethylpyrrolidine (3g): From but-2-enal (1.2 mL, 14 mmol), after 1 d flash chromatography (1:9 Et_2O/hexane), 815 mg (49% over three steps) of **3g** was obtained as a 90:10 mixture of *E*/*Z* isomers (oil): $[\alpha]_D^{20} = +63.4$ (*c* = 1.3, $CHCl_3$). NMR spectroscopic data for the major isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.3 Hz, 6 H), 1.44–1.54 (m, 2 H), 1.79 (dd, *J* = 6.7, 1.6 Hz, 3 H), 2.08–2.15 (m, 2 H), 3.67–3.70 (m, 2 H), 5.69 (dq, *J* = 15.4, 6.7 Hz, 1 H), 6.20 (ddq, *J* = 15.4, 8.9, 1.6 Hz, 1 H), 6.94 (d, *J* = 8.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0, 18.1, 29.2, 54.9, 127.3, 131.0, 134.7 ppm. NMR spectroscopic data for the minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 6.3 Hz, 6 H), 1.44–1.54 (m, 2 H), 1.79 (dd, *J* = 6.7, 1.7 Hz, 3 H), 2.08–2.15 (m, 2 H), 3.67–3.70 (m, 2 H), 5.46–5.57 (m, 1 H), 6.15 (ddq, *J* = 11.1, 9.3, 1.7 Hz, 1 H), 7.20 (d, *J* = 9.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1, 21.3, 30.9, 55.0, 123.4, 128.5, 129.8 ppm. IR (film): ṽ = 2963, 1558, 1448, 1366, 1322, 1214, 1075, 967, 756 cm^{-1}. HRMS: calcd. for $C_{10}H_{19}N_2$ 167.1546; found 167.1548.

General Procedure for the Synthesis of 4-Alkyl-3-aminoazetidin-2-ones 4a–g: *i*Pr_2EtN (2.1 mL, 12 mmol) was added to a solution of hydrazones **3a**–**g** (1 mmol) in dry toluene (5 mL) under argon. The mixture was heated at the appropriate temperature and a solution of **1** (1.8 g, 6 mmol) in dry toluene (15 mL) was added portionwise (six portions of 1 mmol each over 5 h). Simultaneously, six portions of 2-chloro-1-methylpyridinium iodide (281 mg each, 1.1 mmol) were added over the same period of time. The reaction was stirred at the appropriate temperature until TLC indicated total consumption of the starting material. The mixture was then diluted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, concentrated, and the residue purified by flash chromatography. The eluents, yields, and spectral and analytical data for compounds **4a**–**g** are as follows.

***trans*-(3*R*,4*R*)-3-[Benzyl(benzyloxycarbonyl)amino]-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-4-methylazetidin-2-one [(3*R*,4*R*)-4a]:** From **3a** (142 mg, 1 mmol), carrying out the reaction at 80 °C, after 6 h flash chromatography (1:1:12 → 1:1:5 Et_2O/CH_2Cl_2/hexane), 312 mg (74%) of *trans*-(3*R*,4*R*)-**4a** was obtained as an oil: $[\alpha]_D^{24}$ = –62.8 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, [D$_6$]DMSO, 90 °C): δ = 0.97 (d, *J* = 6.3 Hz, 6 H), 1.05 (d, *J* = 6.1 Hz, 3 H), 1.26–1.34 (m, 2 H), 1.87–1.94 (m, 2 H), 3.52–3.58 (m, 3 H), 4.23 (d, *J* = 2.2 Hz, 1 H), 4.50 (d, *J* = 16.0 Hz, 1 H), 4.60 (d, *J* = 16.0 Hz, 1 H), 5.15 (s, 2 H), 7.21–7.34 (m, 10 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 90 °C): δ = 14.8, 18.0, 29.4, 50.0, 54.9, 56.9, 66.4, 66.9, 126.5, 126.6, 127.0, 127.3, 127.8, 136.0, 137.7, 154.7, 163.5 ppm. IR (film): $\tilde{\nu}$ = 2965, 2928, 1755, 1707, 1450, 1421, 1371 cm^{-1}. $C_{25}H_{31}N_3O_3$ (421.53): calcd. C 71.23, H 7.41, N 9.97; found C 71.44, H 7.83, N 9.89.

***trans*-(3*R*,4*R*)-3-[Benzyl(benzyloxycarbonyl)amino]-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-4-isopropylazetidin-2-one [(3*R*,4*R*)-4b]:** From **3b** (168 mg, 1 mmol), carrying out the reaction at 80 °C, after 53 h flash chromatography (1:1:6 Et_2O/CH_2Cl_2/hexane), 297 mg (66%) of *trans*-(3*R*,4*R*)-**4b** was obtained as an oil: $[\alpha]_D^{22}$ = –18.4 (*c* = 0.9, CH_2Cl_2). ^1H NMR (500 MHz, [D$_6$]DMSO, 95 °C): δ = 0.83 (d, *J* = 6.8 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 5.7 Hz, 6 H), 1.31–1.32 (m, 2 H), 1.76 (m, *J* = 6.8 Hz, 1 H), 1.91–1.94 (m, 2 H), 3.35 (dd, *J* = 6.8, 2.5 Hz, 1 H), 3.60–3.67 (m, 2 H), 4.33 (d, *J* = 16.4 Hz, 1 H), 4.57 (d, *J* = 2.5 Hz, 1 H), 4.68 (d, *J* = 16.4 Hz, 1 H), 5.12 (d, *J* = 12.7 Hz, 1 H), 5.16 (d, *J* = 12.7 Hz, 1 H), 7.14–7.31 (m, 10 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 95 °C): δ = 17.7, 17.8, 18.5, 28.5, 29.3, 49.4, 54.9, 63.1, 66.1, 66.5, 126.2, 126.4, 126.6, 127.3, 127.5, 127.7, 127.8, 128.4, 135.9, 137.5, 154.6, 163.8 ppm. IR (film): $\tilde{\nu}$ = 2961, 1753, 1707, 1454, 1240, 1137 cm^{-1}. HRMS: calcd. for $C_{27}H_{35}N_3O_3$ 449.2678; found 449.2658.

***trans*-(3*R*,4*R*)-3-[Benzyl(benzyloxycarbonyl)amino]-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-4-isobutylazetidin-2-one [(3*R*,4*R*)-4c]:** From **3c** (182 mg, 1 mmol), carrying out the reaction at 80 °C, after 37 h flash chromatography (1:1:8 → 1:1:6 Et_2O/CH_2Cl_2/hexane), 335 mg (70%) of *trans*-(3*R*,4*R*)-**4c** was obtained as a solid: m.p. 88–90 °C; $[\alpha]_D^{22}$ = –36.6 (*c* = 1.1, CH_2Cl_2). ^1H NMR (500 MHz, [D$_6$]DMSO, 95 °C): δ = 0.74 (d, *J* = 6.5 Hz, 3 H), 0.77 (d, *J* = 6.5 Hz, 3 H), 0.99 (d, *J* = 6.3 Hz, 6 H), 1.21–1.23 (m, 1 H), 1.29–1.31 (m, 2 H), 1.54–1.61 (m, 2 H), 1.90–1.92 (m, 2 H), 3.53–3.58 (m, 3 H), 4.40 (d, *J* = 16.2 Hz, 1 H), 4.44 (d, *J* = 2.3 Hz, 1 H), 4.64 (d, *J* = 16.2 Hz, 1 H), 5.13 (d, *J* = 12.6 Hz, 1 H), 5.18 (d, *J* = 12.6 Hz, 1 H), 7.13–7.31 (m, 10 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 95 °C): δ = 18.5, 22.3, 22.4, 24.7, 29.8, 50.2, 55.4, 59.8, 66.9, 67.0, 126.9, 127.1, 127.6, 127.9, 128.1, 128.3, 128.9, 136.5, 138.1, 155.2, 164.3 ppm. IR (film): $\tilde{\nu}$ = 2968, 1758, 1701, 1453, 1421 cm^{-1}. $C_{28}H_{37}N_3O_3$ (463.61): calcd. C 72.54, H 8.04, N 9.06; found C 72.25, H 8.07, N 9.32.

***cis*-(3*R*,4*S*)-3-[Benzyl(benzyloxycarbonyl)amino]-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-4-isobutylazetidin-2-one [(3*R*,4*S*)-4c]:** From **3c** (182 mg, 1 mmol), carrying out the reaction at room temp., after 5 d flash chromatography of the crude product (*dr* = 98:2) using silica gel (Merck, 0.040–0.063 mm, 1:4 Et_2O/hexane), 184 mg (40%) of *cis*-(3*R*,4*S*)-**4c** was obtained as an oil: $[\alpha]_D^{25}$ = –36.4 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, [D$_6$]DMSO, 90 °C): δ = 0.78 (d, *J* = 6.6 Hz, 3 H), 0.81 (d, *J* = 6.6 Hz, 3 H), 1.04 (d, *J* = 6.3 Hz, 6 H), 1.09–1.17 (m, 1 H), 1.24–1.39 (m, 3 H), 1.48–1.62 (m, 1 H), 1.84–1.98 (m, 2 H), 3.55–3.66 (m, 2 H), 3.67–3.73 (m, 1 H), 4.51 (s, 2 H), 4.91 (d, *J* = 5.4 Hz, 1 H), 5.12 (s, 2 H), 7.25–7.36 (m, 10 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 90 °C): δ = 18.3, 21.6, 22.3, 24.4, 29.5, 37.3, 50.9, 55.5, 62.4, 62.9, 66.4, 126.5, 127.1, 127.2, 127.3, 127.6, 127.7, 136.0, 137.6, 154.9, 164.6 ppm. IR (film): $\tilde{\nu}$ = 2959, 1755, 1708, 1456, 1371, 1238, 1121, 739, 700 cm^{-1}. HRMS: calcd. for $C_{28}H_{38}N_3O_3$ 464.2913; found 464.2918.

***trans*-(3*R*,4*R*)-3-[Benzyl(benzyloxycarbonyl)amino]-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-4-(2-phenylethyl)azetidin-2-one [(3*R*,4*R*)-4d]:** From **3d** (230 mg, 1 mmol), carrying out the reaction at 80 °C, after 20 h flash chromatography (1:1:15 → 1:1:5 Et_2O/CH_2Cl_2/hexane), 358 mg (70%) of *trans*-(3*R*,4*R*)-**4d** was obtained as an oil: $[\alpha]_D^{22}$ = –28.0 (*c* = 1.1, $CHCl_3$). ^1H NMR (500 MHz, [D$_6$]DMSO, 100 °C): δ = 1.00 (d, *J* = 6.3 Hz, 6 H), 1.23–1.35 (m, 2 H), 1.67–1.73 (m, 1 H), 1.89–1.98 (m, 3 H), 2.57–2.61 (m, 2 H), 3.55–3.59 (m, 3 H), 4.42 (d, *J* = 16.1 Hz, 1 H), 4.45 (d, *J* = 2.3 Hz, 1 H), 4.56 (d, *J* = 16.1 Hz, 1 H), 5.13 (d, *J* = 12.6 Hz, 1 H), 5.17 (d, *J* = 12.6 Hz, 1 H), 7.03–7.38 (m, 15 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 100 °C): δ = 18.4, 29.8, 31.2, 32.2, 50.4, 55.4, 61.0, 66.3, 67.0, 125.7, 126.9, 127.0, 127.5, 127.8, 128.0, 128.2, 128.2, 136.5, 138.0, 141.2, 155.1, 164.1 ppm. IR (film): $\tilde{\nu}$ = 2960, 2926, 1755, 1707, 1454, 1417 cm^{-1}. $C_{32}H_{37}N_3O_3$ (511.65): calcd. C 75.12, H 7.29, N 8.21; found C 75.26, H 7.63, N 8.04.

***cis*-(3*R*,4*S*)-3-[Benzyl(benzyloxycarbonyl)amino]-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-4-(2-phenylethyl)azetidin-2-one [(3*R*,4*S*)-4d]:** From **3d** (230 mg, 1 mmol), carrying out the reaction at room temp., after 4 d flash chromatography (1:6 → 1:2 Et_2O/hexane), 368 mg (72%) of *cis*-(3*R*,4*S*)-**4d** was obtained as an oil: $[\alpha]_D^{26}$ = –33.7 (*c* = 1.2, $CHCl_3$); ^1H NMR (300 MHz, [D$_6$]DMSO, 90 °C): δ = 1.04 (d, *J* = 6.3 Hz, 6 H), 1.24–1.40 (m, 2 H), 1.55–1.67 (m, 1 H), 1.72–1.87 (m, 1 H), 1.89–2.01 (m, 2 H), 2.45–2.55 (m, 1 H), 2.58–2.68 (m, 1 H), 3.60–3.70 (m, 3 H), 4.49 (d, *J* = 15.6 Hz, 1 H), 4.55 (d, *J* = 15.6 Hz, 1 H), 4.91 (d, *J* = 5.1 Hz, 1 H), 5.12 (s, 2 H), 7.05–7.35 (m, 15 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 90 °C): δ = 18.3, 29.5, 30.2, 31.4, 51.0, 55.6, 62.3, 63.9, 66.5, 125.3, 126.6, 127.0, 127.1, 127.3, 127.7, 127.8, 136.0, 137.6, 140.8, 155.0, 164.5 ppm. IR (film): $\tilde{\nu}$ = 2967, 1760, 1712, 1458, 1243, 1140, 703 cm^{-1}. HRMS: calcd. for $C_{32}H_{38}N_3O_3$ 512.2913; found 512.2879.

***trans*-(3*R*,4*R*)-3-[Benzyl(benzyloxycarbonyl)amino]-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-4-pentylazetidin-2-one [(3*R*,4*R*)-4e]:** From **3e** (196 mg, 1 mmol), carrying out the reaction at 80 °C, after 10 h flash chromatography (1:8 → 1:2 Et_2O/hexane), 282 mg (59%) of *trans*-(3*R*,4*R*)-**4e** was obtained as an oil: $[\alpha]_D^{22}$ = –39.7 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, [D$_6$]DMSO, 90 °C): δ = 0.82 (t, *J* = 7.0 Hz, 3 H), 0.99 (d, *J* = 6.3 Hz, 6 H), 1.13–1.39 (m, 9 H), 1.59–1.66 (m, 1 H), 1.87–1.97 (m, 2 H), 3.46–3.51 (m, 1 H), 3.54–3.60 (m, 2 H), 4.42 (d, *J* = 2.3 Hz, 1 H), 4.44 (d, *J* = 15.9 Hz, 1 H), 4.61 (d, *J* = 15.9 Hz, 1 H), 5.13 (d, *J* = 12.6 Hz, 1 H), 5.18 (d, *J* = 12.6 Hz, 1 H), 7.21–7.35 (m, 10 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 90 °C): δ = 12.9, 17.8, 21.1, 23.9, 29.3, 29.8, 30.5, 49.6, 54.9, 60.8, 65.7, 66.4, 126.3, 126.4, 127.0, 127.2, 127.6, 135.9, 137.5, 154.6, 163.6 ppm. IR (film): $\tilde{\nu}$ = 2961, 1753, 1707 cm^{-1}.

$C_{29}H_{39}N_3O_3$ (477.64): calcd. C 72.92, H 8.23, N 8.80; found C 73.05, H 8.38, N 8.68.

***cis*-(3*R*,4*S*)-3-[Benzyl(benzyloxycarbonyl)amino]-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-4-pentylazetidin-2-one [(3*R*,4*S*)-4e]:** From **3e** (196 mg, 1 mmol), carrying out the reaction at room temp., after 4 d flash chromatography (1:4 Et_2O/hexane) of the crude product (*dr* = 87:13), 196 mg (41%) of *cis*-(3*R*,4*S*)-**4e** was obtained as an oil: $[\alpha]_D^{25}$ = –37.0 (*c* = 1.4, $CHCl_3$). ^1H NMR (300 MHz, [D$_6$]DMSO, 90 °C): δ = 0.84 (t, *J* = 6.6 Hz, 3 H), 1.03 (d, *J* = 6.3 Hz, 6 H), 1.19–1.49 (m, 10 H), 1.85–1.97 (m, 2 H), 3.58–3.65 (m, 3 H), 4.48 (d, *J* = 15.9 Hz, 1 H), 4.54 (d, *J* = 15.9 Hz, 1 H), 4.90 (d, *J* = 5.1 Hz, 1 H), 5.12 (s, 2 H), 7.23–7.31 (m, 10 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 90 °C): δ = 13.1, 18.3, 21.1, 24.7, 28.2, 29.4, 30.7, 50.9, 55.5, 62.3, 64.7, 66.4, 126.5, 127.0, 127.1, 127.3, 127.6, 127.7, 136.0, 137.6, 154.9, 164.4 ppm. IR (film): $\tilde{\nu}$ = 2967, 2869, 1755, 1707, 1232, 748, 700 cm^{-1}. HRMS: calcd. for $C_{29}H_{40}N_3O_3$ 478.3070; found 478.3066.

***trans*-(3*R*,4*S*)- and *cis*-(3*R*,4*R*)-3-[Benzyl(benzyloxycarbonyl)amino]-4-(benzyloxymethyl)-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]azetidin-2-one [(3*R*,4*S*)-4f and (3*R*,4*R*)-4f]:** From **3f** (246 mg, 1 mmol), carrying out the reaction at 80 °C, after 38 h flash chromatography (10:1 toluene/EtOAc), 348 mg (66%) of **4f** was obtained as a mixture of *trans*-(3*R*,4*S*)-**4f** and *cis*-(3*R*,4*R*)-**4f** in a 54:46 ratio. Medium-pressure liquid chromatography (6:1 toluene/EtOAc) allowed the isolation of both pure isomers as oils.

***trans*-(3*R*,4*S*)-4f:** $[\alpha]_D^{25}$ = –41.1 (*c* = 0.9, CH_2Cl_2). ^1H NMR (300 MHz, [D$_6$]DMSO, 90 °C): δ = 0.99 (d, *J* = 6.4 Hz, 6 H), 1.25–1.37 (m, 2 H), 1.87–1.98 (m, 2 H), 3.42 (dd, *J* = 10.8, 3.3 Hz, 1 H), 3.53–3.64 (m, 2 H), 3.62 (dd, *J* = 10.8, 3.3 Hz, 1 H), 3.75–3.78 (m, 1 H), 4.36 (d, *J* = 12.0 Hz, 1 H), 4.43 (d, *J* = 12.0 Hz, 1 H), 4.48–4.59 (m, 2 H), 4.68 (d, *J* = 2.4 Hz, 1 H), 5.15 (s, 2 H), 7.23–7.35 (m, 15 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 95 °C): δ = 17.9, 29.6, 50.3, 55.6, 60.5, 61.5, 65.5, 66.6, 72.1, 126.6, 126.7, 126.9, 127.0, 127.1, 127.4, 127.8, 127.9, 128.0, 136.1, 137.5, 137.7, 154.8, 164.1 ppm. IR (film): $\tilde{\nu}$ = 1757, 1718, 1376, 1241, 1114, 748, 709 cm^{-1}. HRMS: calcd. for $C_{32}H_{37}N_3O_4$ 527.2784; found 527.2795.

***cis*-(3*R*,4*R*)-4f:** $[\alpha]_D^{26}$ = –32.3 (*c* = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, [D$_6$]DMSO, 95 °C): δ = 1.01 (d, *J* = 6.3 Hz, 6 H), 1.21–1.36 (m, 2 H), 1.83–1.97 (m, 2 H), 3.45 (dd, *J* = 10.7, 5.3 Hz, 1 H), 3.51–3.66 (m, 3 H), 3.90 (q, *J* = 5.3 Hz, 1 H), 4.37 (s, 2 H), 4.41 (d, *J* = 15.9 Hz, 1 H), 4.51 (d, *J* = 15.9 Hz, 1 H), 4.93 (d, *J* = 5.3 Hz, 1 H), 5.08 (s, 2 H), 7.14–7.37 (m, 15 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 95 °C): δ = 18.1, 29.2, 50.8, 55.1, 61.5, 63.5, 66.4, 67.6, 72.2, 126.5, 126.9, 127.1, 127.3, 127.6, 127.7, 136.0, 137.5, 137.6, 154.8, 164.1 ppm. IR (film): $\tilde{\nu}$ = 1759, 1704, 1379, 1244, 1101, 708 cm^{-1}. $C_{32}H_{37}N_3O_4$ (527.65): calcd. C 72.84, H 7.07, N 7.96; found C 73.06, H 6.88, N 7.58.

***cis*-(3*R*,4*R*)-3-[Benzyl(benzyloxycarbonyl)amino]-4-(benzyloxymethyl)-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]azetidin-2-one [(3*R*,4*R*)-4f]:** From **3f** (246 mg, 1 mmol), carrying out the reaction at 40 °C, after 29 h flash chromatography (10:1 toluene/EtOAc), 501 mg (95%) of *cis*-(3*R*,4*R*)-**4f** was obtained, identical to the product described above.

***cis*-(3*R*,4*S*)-3-[Benzyl(benzyloxycarbonyl)amino]-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-4-(prop-1-enyl)azetidin-2-one [(3*R*,4*S*)-4g]:** From **3g** (166 mg, 1 mmol), carrying out the reaction at 80 °C, after 55 h flash chromatography (1:4 → 1:1 Et_2O/hexane), 301 mg (67%) of *cis*-(3*R*,4*S*)-**4g** was obtained as an oil: $[\alpha]_D^{26}$ = –7.8 (*c* = 1.2, $CHCl_3$). ^1H NMR (300 MHz, [D$_6$]DMSO, 90 °C): δ = 1.01 (d, *J* = 6.3 Hz, 6 H), 1.26–1.31 (m, 2 H), 1.53 (d, *J* = 6.3 Hz, 3 H), 1.84–1.94 (m, 2 H), 3.51–3.57 (m, 2 H), 4.15 (dd, *J* = 8.5, 5.2 Hz, 1 H), 4.44 (d, *J* = 15.6 Hz, 1 H), 4.51 (d, *J* = 15.6 Hz, 1 H), 4.86 (d, *J* = 5.2 Hz, 1 H), 5.11 (s, 2 H), 5.22–5.30 (m, 1 H), 5.47–5.59 (m, 1 H), 7.23–7.32 (m, 10 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 90 °C): δ = 16.9, 18.0, 29.1, 50.7, 55.2, 63.3, 66.2, 66.6, 125.5, 126.5, 127.0, 127.1, 127.2, 127.5, 127.6, 127.7, 131.2, 136.0, 137.3, 154.7, 164.1 ppm. IR (film): $\tilde{\nu}$ = 2963, 1756, 1707, 1657, 1453, 1233 cm^{-1}. HRMS: calcd. for $C_{27}H_{33}N_3O_3$ 447.2522; found 447.2539.

2-(Benzyloxy)-*N*-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-*N*-(3-phenylprop-1-enyl)acetamide (9): Bn_3N (1.1 g, 4 mmol) was added to a solution of **3d** (115 mg, 0.5 mmol) in dry toluene (2.5 mL) under argon. The mixture was heated to 60 °C and a solution of **5** (0.33 mL, 2 mmol) in dry toluene (5 mL) was added over 4 h (syringe pump). The mixture was then washed with H_2O and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (1:1:6 Et_2O/CH_2Cl_2/hexane) gave 140 mg (74%) of **9** as a 92:8 mixture of *E*/*Z* isomers (oil): NMR spectroscopic data for the major isomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.0 Hz, 3 H), 1.04 (d, *J* = 6.0 Hz, 3 H), 1.30–1.44 (m, 2 H), 1.94–2.00 (m, 2 H), 3.43 (d, *J* = 7.5 Hz, 2 H), 3.36–3.50 (m, 1 H), 3.58–3.65 (m, 1 H), 4.19 (d, *J* = 17.0 Hz, 1 H), 4.64 (d, *J* = 17.0 Hz, 1 H), 4.68 (s, 2 H), 5.60 (dt, *J* = 14.5, 7.0 Hz, 1 H), 6.68 (d, *J* = 14.5 Hz, 1 H), 7.19–7.41 (m, 10 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.3, 19.3, 31.5, 32.5, 37.1, 53.0, 57.3, 68.2, 73.2, 115.4, 125.2, 126.2, 127.9, 128.1, 128.4, 128.5, 128.6, 138.0, 140.7, 173.0 ppm. IR (film): $\tilde{\nu}$ = 2961, 1692, 1658, 1259, 1128, 738, 698 cm^{-1}. HRMS: calcd. for $C_{24}H_{31}N_2O_2$ 379.2386; found 379.2370.

General Procedure for the Oxidative Cleavage of N–N Bonds. Synthesis of Compounds 10a–f: MMPP·6H_2O (730 mg, 1.25 mmol) was added to a solution of **4a**–**f** (1 mmol) in CH_3OH (0.4 mL) and the mixture was stirred at room temp. for 1 h. The mixture was then diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ and H_2O, dried (Na_2SO_4), filtered, concentrated, and the residue purified by flash chromatography. The eluents, yields, and spectral and analytical data for compounds **10a**–**f** are as follows.

***trans*-(3*R*,4*R*)-3-[Benzyl(benzyloxycarbonyl)amino]-4-methylazetidin-2-one [(3*R*,4*R*)-10a]:** From *trans*-(3*R*,4*R*)-**4a**, flash chromatography (1:1:1 Et_2O/CH_2Cl_2/hexane) and further purification using medium-pressure liquid chromatography (1:1 toluene/AcOEt) gave 292 mg (90%) of *trans*-(3*R*,4*R*)-**10a** as an oil: $[\alpha]_D^{24}$ = +18.4 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, [D$_6$]DMSO, 90 °C): δ = 1.06 (d, *J* = 6.1 Hz, 3 H), 3.51–3.53 (m, 1 H), 4.25 (d, *J* = 2.3 Hz, 1 H), 4.49 (d, *J* = 15.8 Hz, 1 H), 4.56 (d, *J* = 15.8 Hz, 1 H), 5.13 (s, 2 H), 7.23–7.35 (m, 10 H), 7.82 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 90 °C): δ = 18.3, 50.1, 66.5, 70.3, 126.6, 126.7, 127.0, 127.3, 127.8, 127.8, 136.0, 137.8, 154.7, 164.8 ppm. IR (film): $\tilde{\nu}$ = 3255 (br), 1767, 1701, 1454, 1417, 1369 cm^{-1}. HRMS: calcd. for $C_{19}H_{20}N_2O_3$ 324.1474; found 324.1457.

***trans*-(3*R*,4*R*)-3-[Benzyl(benzyloxycarbonyl)amino]-4-isopropylazetidin-2-one [(3*R*,4*R*)-10b]:** From *trans*-(3*R*,4*R*)-**4b**, flash chromatography (1:1 → 5:1 Et_2O/hexane) gave 253 mg (72%) of *trans*-(3*R*,4*R*)-**10b** as an oil: $[\alpha]_D^{22}$ = +24.4 (*c* = 1.1, CH_2Cl_2). ^1H NMR (300 MHz, [D$_6$]DMSO, 95 °C): δ = 0.77 (d, *J* = 7.2 Hz, 3 H), 0.79 (d, *J* = 7.2 Hz, 3 H), 1.53–1.65 (m, 1 H), 3.21 (dd, *J* = 7.5, 2.7 Hz, 1 H), 4.36 (d, *J* = 16.2 Hz, 1 H), 4.52 (d, *J* = 2.7 Hz, 1 H), 4.65 (d, *J* = 16.2 Hz, 1 H), 5.13 (s, 2 H), 7.23–7.32 (m, 10 H), 8.02 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 95 °C): δ = 17.5, 17.8, 30.4, 49.6, 59.9, 66.5, 67.0, 126.6, 127.0, 127.3, 127.3, 127.8, 135.9, 137.7, 154.7, 165.4 ppm. IR (film): $\tilde{\nu}$ = 3277, 2967, 1776, 1704,

1426, 1100, 743 cm^{-1}. HRMS: calcd. for $C_{21}H_{25}N_2O_3$ 353.1865; found 353.1865.

***trans*-(3*R*,4*R*)-3-[Benzyl(benzyloxycarbonyl)amino]-4-isobutylazetidin-2-one [(3*R*,4*R*)-10c]:** From *trans*-(3*R*,4*R*)-**4c**, flash chromatography (1:1 → 4:1 Et_2O/hexane) gave 311 mg (85%) of *trans*-(3*R*,4*R*)-**10c** as an oil: $[\alpha]_D^{22}$ = +32.5 (*c* = 1.3, CH_2Cl_2). ^1H NMR (300 MHz, [D$_6$]DMSO, 95 °C): δ = 0.73 (d, *J* = 7.0 Hz, 3 H), 0.75 (d, *J* = 7.0 Hz, 3 H), 1.13–1.36 (m, 2 H), 1.42–1.51 (m, 1 H), 3.42–3.47 (m, 1 H), 4.38 (d, *J* = 2.5 Hz, 1 H), 4.44 (d, *J* = 15.9 Hz, 1 H), 4.59 (d, *J* = 15.9 Hz, 1 H), 5.12 (d, *J* = 12.6 Hz, 1 H), 5.16 (d, *J* = 12.6 Hz, 1 H), 7.21–7.37 (m, 10 H), 7.93 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 95 °C): δ = 21.9, 22.6, 25.2, 42.6, 50.4, 53.2, 67.0, 69.9, 127.1, 127.6, 127.8, 128.3, 136.5, 138.3, 155.2, 165.8 ppm. IR (film): ṽ = 3293, 2959, 1776, 1704, 1458, 1428, 1243, 743, 703 cm^{-1}. $C_{22}H_{26}N_2O_3$ (366.45): calcd. C 72.11, H 7.15, N 7.64; found C 72.32, H 7.02, N 7.45.

***cis*-(3*R*,4*S*)-3-[Benzyl(benzyloxycarbonyl)amino]-4-isobutylazetidin-2-one [(3*R*,4*S*)-10c]:** From *cis*-(3*R*,4*S*)-**4c**, flash chromatography (1:1 Et_2O/hexane) gave 341 mg (93%) of *cis*-(3*R*,4*S*)-**10c** as an oil: $[\alpha]_D^{22}$ = –28.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, [D$_6$]DMSO, 90 °C): δ = 0.74–0.77 (m, 6 H), 0.96–1.15 (m, 2 H), 1.45–1.50 (m, 1 H), 3.62–3.65 (m, 1 H), 4.50 (d, *J* = 15.3 Hz, 1 H), 4.55 (d, *J* = 15.3 Hz, 1 H), 4.91 (dd, *J* = 5.0, 1.5 Hz, 1 H), 5.10 (d, *J* = 13.0 Hz, 1 H), 5.12 (d, *J* = 13.0 Hz, 1 H), 7.23–7.35 (m, 10 H), 8.07 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 90 °C): δ = 21.3, 22.4, 24.5, 38.3, 50.6, 52.2, 66.4, 126.5, 127.2, 127.3, 127.4, 127.6, 127.7, 136.0, 137.8, 154.9, 165.0 ppm. IR (film): ṽ = 3291 (br), 2955, 1764, 1703, 1455, 740, 697 cm^{-1}. HRMS: calcd. for $C_{22}H_{27}N_2O_3$ 367.2022; found 367.2015.

***trans*-(3*R*,4*R*)-3-[Benzyl(benzyloxycarbonyl)amino]-4-(2-phenylethyl)azetidin-2-one [(3*R*,4*R*)-10d]:** From *trans*-(3*R*,4*R*)-**4d**, flash chromatography (1:1:2 Et_2O/CH_2Cl_2/hexane) gave 302 mg (73%) of *trans*-(3*R*,4*R*)-**10d** as an oil: $[\alpha]_D^{22}$ = +26.4 (*c* = 0.9, $CHCl_3$). ^1H NMR (300 MHz, [D$_6$]DMSO, 90 °C): δ = 1.66–1.73 (m, 2 H), 2.41–2.58 (m, 2 H), 3.45 (td, *J* = 6.3, 2.3 Hz, 1 H), 4.42 (d, *J* = 2.3 Hz, 1 H), 4.45 (d, *J* = 15.9 Hz, 1 H), 4.55 (d, *J* = 15.9 Hz, 1 H), 5.13 (s, 2 H), 7.04–7.35 (m, 15 H), 7.98 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 90 °C): δ = 31.0, 34.4, 50.0, 53.7, 66.5, 68.9, 125.2, 126.6, 126.7, 127.0, 127.3, 127.5, 127.7, 127.8, 135.9, 137.6, 140.6, 154.6, 165.1 ppm. IR (film): ṽ = 3240 (br), 1767, 1699, 1454, 1420 cm^{-1}. HRMS: calcd. for $C_{26}H_{26}N_2O_3$ 414.1943; found 414.1947.

***cis*-(3*R*,4*S*)-3-[Benzyl(benzyloxycarbonyl)amino]-4-(2-phenylethyl)azetidin-2-one [(3*R*,4*S*)-10d]:** From *cis*-(3*R*,4*S*)-**4d**, flash chromatography (1:1 Et_2O/hexane) gave 377 mg (91%) of *cis*-(3*R*,4*S*)-**10d** as an oil: $[\alpha]_D^{24}$ = –40.6 (*c* = 1.5, $CHCl_3$). ^1H NMR (300 MHz, [D$_6$]DMSO, 90 °C): δ = 1.49–1.56 (m, 2 H), 2.37–2.61 (m, 2 H), 3.56–3.62 (m, 1 H), 4.54 (s, 2 H), 4.91 (dd, *J* = 5.1, 1.5 Hz, 1 H), 5.10 (s, 2 H), 7.02–7.35 (m, 15 H), 8.15 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 90 °C): δ = 31.2, 31.2, 50.7, 53.3, 66.2, 66.4, 125.2, 126.5, 127.1, 127.3, 127.5, 127.6, 127.7, 135.9, 137.8, 140.7, 154.9, 164.9 ppm. IR (film): ṽ = 3301 (br), 1767, 1705, 1454, 1412, 1235, 745, 700 cm^{-1}. HRMS: calcd. for $C_{26}H_{27}N_2O_3$ 415.2022; found 415.2018.

***trans*-(3*R*,4*R*)-3-[Benzyl(benzyloxycarbonyl)amino]-4-pentylazetidin-2-one [(3*R*,4*R*)-10e]:** From *trans*-(3*R*,4*R*)-**4e**, flash chromatography (1:1:2 Et_2O/CH_2Cl_2/hexane) gave 281 mg (74%) of *trans*-(3*R*,4*R*)-**10e** as an oil: $[\alpha]_D^{22}$ = +27.6 (*c* = 0.9, $CHCl_3$). ^1H NMR (500 MHz, [D$_6$]DMSO, 90 °C): δ = 0.82 (t, *J* = 7.1 Hz, 3 H), 1.13–1.23 (m, 6 H), 1.34–1.37 (m, 2 H), 3.39–3.41 (m, 1 H), 4.37 (d, *J* = 2.4 Hz, 1 H), 4.47 (d, *J* = 15.9 Hz, 1 H), 4.57 (d, *J* = 15.9 Hz, 1 H), 5.09–5.16 (m, 2 H), 7.23–7.34 (m, 10 H), 7.94 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 90 °C): δ = 14.0, 22.2, 25.4, 31.3, 33.6, 50.8, 55.1, 67.5, 69.8, 127.6, 127.6, 128.0, 128.3, 128.6, 128.7, 136.9, 138.7, 155.6, 166.2 ppm. IR (film): ṽ = 3293 (br), 2930, 1767, 1705, 1456, 1421 cm^{-1}. HRMS: calcd. for $C_{23}H_{28}N_2O_3$ 380.2100; found 380.2103.

***cis*-(3*R*,4*S*)-3-[Benzyl(benzyloxycarbonyl)amino]-4-pentylazetidin-2-one [(3*R*,4*S*)-10e]:** From *cis*-(3*R*,4*S*)-**4e**, flash chromatography (1:1:2 Et_2O/CH_2Cl_2/hexane) gave 320 mg (84%) of *cis*-(3*R*,4*S*)-**10e** as an oil: $[\alpha]_D^{25}$ = –26.5 (*c* = 1.2, $CHCl_3$). ^1H NMR (300 MHz, [D$_6$]-DMSO, 90 °C): δ = 0.83 (t, *J* = 6.6 Hz, 3 H), 1.13–1.39 (m, 8 H), 3.49–3.58 (m, 1 H), 4.53 (s, 2 H), 4.89 (dd, *J* = 4.8, 1.2 Hz, 1 H), 5.11 (s, 2 H), 7.22–7.36 (m, 10 H), 8.08 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 90 °C): δ = 13.1, 21.2, 24.7, 29.3, 30.5, 50.6, 53.9, 66.2, 66.4, 126.5, 127.1, 127.3, 127.6, 127.7, 136.0, 137.9, 154.9, 164.9 ppm. IR (film): ṽ = 3293 (br), 2925, 1765, 1704, 1455, 1409, 1230 cm^{-1}. HRMS: calcd. for $C_{23}H_{29}N_2O_3$ 381.2178; found 381.2169.

***cis*-(3*R*,4*R*)-3-[Benzyl(benzyloxycarbonyl)amino]-4-(benzyloxymethyl)azetidin-2-one [(3*R*,4*R*)-10f]:** From *cis*-(3*R*,4*R*)-**4f**, flash chromatography (1:1 → 4:1 Et_2O/hexane) gave 318 mg (74%) of *cis*-(3*R*,4*R*)-**10f** as an oil: $[\alpha]_D^{27}$ = –29.5 (*c* = 0.9, CH_2Cl_2). ^1H NMR (300 MHz, [D$_6$]DMSO, 95 °C): δ = 3.33–3.42 (m, 2 H), 3.83 (dt, *J* = 6.2, 5.2 Hz, 1 H), 4.35 (s, 2 H), 4.45 (d, *J* = 15.6 Hz, 1 H), 4.52 (d, *J* = 15.6 Hz, 1 H), 4.93 (dd, *J* = 5.2, 1.3 Hz, 1 H), 5.07 (s, 2 H), 7.21–7.37 (m, 15 H), 8.12 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 95 °C): δ = 50.6, 52.8, 65.5, 66.4, 69.3, 72.1, 126.5, 126.8, 126.9, 127.1, 127.3, 127.6, 127.6, 127.7, 135.9, 137.7, 154.8, 164.9 ppm. IR (film): ṽ = 1767, 1701, 1370, 1251, 1094 cm^{-1}. HRMS: calcd. for $C_{26}H_{27}N_2O_4$ 431.1971; found 431.1971.

***cis*-(3*R*,4*S*)-3-[Benzyl(benzyloxycarbonyl)amino]-4-(prop-1-enyl)azetidin-2-one [(3*R*,4*S*)-10g]:** From *cis*-(3*R*,4*S*)-**4g**, following the general procedure but carrying out the reaction at 0 °C. Flash chromatography (4:1 Et_2O/hexane) gave 210 mg (60%) of *cis*-(3*R*,4*S*)-**10g** as an oil. *cis*-(3*R*,4*R*)-**11** (115 mg, 33%) was also isolated as an oil.

***cis*-(3*R*,4*S*)-10g:** $[\alpha]_D^{20}$ = +11.9 (*c* = 1.3, $CHCl_3$). ^1H NMR (500 MHz, [D$_6$]DMSO, 90 °C): δ = 1.51 (d, *J* = 6.5 Hz, 3 H), 4.10 (t, *J* = 5.5 Hz, 1 H), 4.44 (d, *J* = 15.5 Hz, 1 H), 4.49 (d, *J* = 15.5 Hz, 1 H), 4.95 (d, *J* = 5.5 Hz, 1 H), 5.10 (s, 2 H), 5.11–5.19 (m, 1 H), 5.42–5.49 (m, 1 H), 7.14–7.35 (m, 10 H), 8.10 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 90 °C): δ = 16.8, 50.6, 55.1, 66.3, 67.8, 126.5, 127.1, 127.3, 127.4, 127.5, 127.7, 129.1, 136.1, 137.8, 154.8, 164.9 ppm. IR (film): ṽ = 3292 (br), 3031, 2919, 1766, 1703, 1450, 1363, 969, 698 cm^{-1}. HRMS: calcd. for $C_{21}H_{23}N_2O_3$ 351.1709; found 351.1710.

***cis*-(3*R*,4*R*)-11:** $[\alpha]_D^{20}$ = –23.7 (*c* = 0.7, $CHCl_3$). ^1H NMR (500 MHz, [D$_6$]DMSO, 90 °C): δ = 0.99 (d, *J* = 5.0 Hz, 3 H), 2.46–2.48 (m, 2 H), 3.38 (t, *J* = 5.5 Hz, 1 H), 4.50 (d, *J* = 15.5 Hz, 1 H), 4.59 (d, *J* = 15.5 Hz, 1 H), 5.00 (d, *J* = 5.5 Hz, 1 H), 5.14 (s, 2 H), 7.25–7.40 (m, 10 H), 8.30 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 90 °C): δ = 16.2, 50.4, 50.7, 55.6, 56.8, 66.2, 66.6, 126.6, 127.1, 127.3, 127.4, 127.7, 127.8, 135.9, 137.7, 154.7, 164.9 ppm. IR (film): ṽ = 3295, 2924, 1771, 1703, 1455, 1257, 1025, 700 cm^{-1}. HRMS: calcd. for $C_{21}H_{23}N_2O_4$ 367.1658; found 367.1648.

***cis*-(3*R*,4*R*)-3-[Benzyl(benzyloxycarbonyl)amino]-4-(1,2-epoxypropyl)azetidin-2-one (11):** From *cis*-(3*R*,4*S*)-**4g**, following the general procedure but adding 1.5 g (2.6 mmol) of MMPP. Flash chromatography (4:1→8:1 Et_2O/hexane) gave 224 mg (61%) of **11**, identical to the product described above.

***trans*-(3*R*,4*R*)-3-Amino-4-methylazetidin-2-one (12):** 20% $Pd(OH)_2$/C (10 mg) was added to a solution of *trans*-(3*R*,4*R*)-**10a** (324 mg,

1 mmol) in 20:1 dioxane/H_2O (25 mL). The mixture was stirred under H_2 (6 bar) for 6 h at room temp., filtered through a Celite pad, and concentrated. Purification of the residue by flash chromatography (15:1→8:1 CH_2Cl_2/CH_3OH) gave 75 mg (75%) of *trans*-(3*R*,4*R*)-**12** as an oil: $[\alpha]_D^{22}$ = +63.5 (*c* = 0.7, $CHCl_3$). ^1H NMR (300 MHz, CD_3OD): δ = 1.33 (d, *J* = 6.1 Hz, 3 H), 3.42 (qd, *J* = 6.0, 2.0 Hz, 1 H), 3.55 (d, *J* = 2.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 19.2, 55.9, 67.5, 172.9 ppm. IR (film): $\tilde{\nu}$ = 3283 (br), 2874, 1748, 1377, 1352 cm^{-1}.

***trans*-(3*R*,4*R*)-3-[(*tert*-Butoxycarbonyl)amino]-4-methylazetidin-2-one (13):** Et_3N (0.28 mL, 2 mmol) was added to a solution of *trans*-(3*R*,4*R*)-**12** (100 mg, 1 mmol) in CH_3OH (2 mL). A solution of Boc_2O (436 mg, 2 mmol) in CH_3OH (2 mL) was added dropwise and the mixture was stirred at room temp. for 2 h. The mixture was concentrated, diluted with CH_2Cl_2, and washed with H_2O and brine. The organic layer was dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (15:1 CH_2Cl_2/MeOH) gave 144 mg (72%) of *trans*-(3*R*,4*R*)-**13** as a white solid: m.p. 132–134 °C. $[\alpha]_D^{22}$ = +59.0 (*c* = 1.9, CH_3OH) [literature value for (3*S*,4*S*)-**13**:[40] $[\alpha]_D^{22}$ = –64.2 (*c* = 0.85, CH_3OH)]. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.1 Hz, 3 H), 1.41 (s, 9 H), 3.67 (qd, *J* = 6.1, 2.1 Hz, 1 H), 4.23 (d, *J* = 7.0 Hz, 1 H), 5.50 (d, *J* = 7.0 Hz, 1 H), 6.59 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 28.2, 54.1, 64.6, 80.2, 155.0, 167.4 ppm. IR (film): $\tilde{\nu}$ = 3260 (br), 2982, 2920, 1726, 1695, 1530, 1449, 1385, 1371, 1072, 880 cm^{-1}. HRMS: calcd. for $C_9H_{17}N_2O_3$ 201.1239; found 201.1249.

***cis*-(3*R*,4*R*)-3-[(Benzyloxycarbonyl)amino]-4-(hydroxymethyl)-azetidin-2-one (14):** Ammonium formate (780 mg, 12 mmol) and 10% Pd/C (1.5 g) were added to a solution of *cis*-(3*R*,4*R*)-**10f** (430 mg, 1 mmol) in CH_3OH (20 mL). The reaction mixture was stirred under reflux for 1 h, filtered through a Celite pad, and concentrated. The residue was dissolved in CH_3OH (2 mL) and Et_3N (280 μL, 2 mmol) and benzyl chloroformate (300 μL, 2 mmol) were added. The mixture was stirred at room temp. for 5 h and then concentrated. The residue was dissolved in EtOAc and washed with H_2O. The organic layer was dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (EtOAc) gave 138 mg (55%, two steps) of *cis*-(3*R*,4*R*)-**14** as a white solid: m.p. 124–126 °C; $[\alpha]_D^{25}$ = –7.4 (*c* = 1.0, $CHCl_3$) [literature value for (3*S*,4*S*)-**14**:[41] $[\alpha]_D^{22}$ = +8.6 (*c* = 0.9, $CHCl_3$); for (3*S*,4*S*)-**14**:[43] $[\alpha]_D^{22}$ = +8.7 (*c* = 0.55, $CHCl_3$); for (3*S*,4*S*)-**14**:[44] $[\alpha]_D^{22}$ = +9.0 (*c* = 0.93, $CHCl_3$)]. ^1H NMR (300 MHz, [D_6]DMSO, 90 °C): δ = 3.49–3.64 (m, 2 H), 3.69 (ddd, *J* = 6.1, 5.1, 4.4 Hz, 1 H), 4.49 (t, *J* = 5.1 Hz, 1 H), 4.88 (ddd, *J* = 6.2, 5.1, 1.1 Hz, 1 H), 5.06 (d, *J* = 12.6 Hz, 1 H), 5.10 (d, *J* = 12.6 Hz, 1 H), 7.28–7.40 (m, 5 H), 7.87 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 90 °C): δ = 53.7, 59.1, 60.3, 65.4, 127.1, 127.3, 127.8, 136.5, 155.2, 167.0 ppm. HRMS: calcd. for $C_{12}H_{14}N_2O_4$ 250.0954; found 250.0954.

***cis*-(3*R*,4*S*)-3-[(*tert*-Butoxycarbonylamino)]-4-(2-phenylethyl)-azetidin-2-one (15):** Ammonium formate (520 mg, 8 mmol) and 10% Pd/C (1.0 g) were added to a solution of *cis*-(3*R*,4*S*)-**10d** (414 mg, 1 mmol) in CH_3OH (20 mL). The reaction mixture was stirred under reflux for 1 h, filtered through a Celite pad, and concentrated. The crude residue was solved in CH_3OH (2.6 mL) and Et_3N (280 μL, 2 mmol) was added. Then a solution of Boc_2O (436 mg, 2 mmol) in CH_3OH (1 mL) was added dropwise and the mixture stirred at room temp. for 4 h. The mixture was concentrated, diluted with CH_2Cl_2, washed with H_2O and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by flash chromatography (1:1 toluene/AcOEt) gave 122 mg (42%, two steps) of *cis*-(3*R*,4*S*)-**15** as a white solid: m.p. 134–136 °C; $[\alpha]_D^{26}$ = –56.5 (*c* = 1.1, CH_2Cl_2) [literature value for (3*S*,4*R*)-**15**:[42] $[\alpha]_D^{25}$ = +62.1 (*c* = 1.0, CH_2Cl_2)]. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 1.70–1.82 (m, 1 H), 1.87–1.98 (m, 1 H), 2.57–2.77 (m, 2 H), 3.76–3.83 (m, 1 H), 5.06 (dd, *J* = 8.3, 4.5 Hz, 1 H), 5.17 (d, *J* = 8.3 Hz, 1 H), 5.82 (br. s, 1 H), 7.64–7.32 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4, 32.6, 32.7, 55.0, 60.6, 80.7, 126.5, 128.5, 128.8, 140.9, 155.3, 167.7 ppm. HRMS: calcd. for $C_{16}H_{23}N_2O_3$ 291.1709; found 291.1705.

***cis*-(3*R*,4*R*)-3-[Benzyl(benzyloxycarbonyl)amino]-4-(benzyloxymethyl)-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]azetidin-2-one [(3*R*,4*R*)-4f] from (3*R*,4*S*)-4g:** Compound *cis*-(3*R*,4*S*)-**4g** (144 mg, 0.32 mmol) was treated with ozone in CH_2Cl_2 (3 mL) at –78 °C until a permanent blue color appeared. SMe_2 (0.42 mL, 3.2 mmol) was added, the solvent was evaporated, and the crude aldehyde was dissolved in MeOH (2 mL). $NaBH_4$ (25 mg, 0.64 mmol) was added, the mixture was stirred at room temp. until TLC indicated total consumption of the starting material, and concentrated. The residue was diluted with EtOAc and washed with H_2O. The organic layer was dried (Na_2SO_4) and concentrated. The residue was dissolved in THF (3 mL) and NaH (33 mg, 0.8 mmol) and BnBr (0.12 mL, 0.96 mmol) were added. The mixture was stirred at room temp. for 3 h and then MeOH (3 mL) was added. The mixture was partitioned between H_2O and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (1:1 Et_2O/hexane) gave 71 mg of (3*R*,4*R*)-**4f** (43%, three steps). The spectral and analytical data for this compound are identical to those of *cis*-(3*R*,4*R*)-**4f** obtained directly by cycloaddition of **3f** with *N*-benzyl-*N*-(benzyloxycarbonyl)aminoketene as described above.

***trans*-(3*R*,4*R*)-3-Amino-4-isobutylazetidin-2-one (16):** Ammonium formate (520 mg, 8 mmol) and 10% Pd/C (0.5 g) were added to a solution of *trans*-(3*R*,4*R*)-**10c** (366 mg, 1 mmol) in CH_3OH (20 mL). The reaction mixture was stirred under reflux for 1 h, filtered through a Celite pad, and concentrated. Purification of the residue by flash chromatography (13:1 CH_2Cl_2/CH_3OH) gave 102 mg (72%) of *trans*-(3*R*,4*R*)-**16** as an oil: $[\alpha]_D^{22}$ = +57.3 (*c* = 1.3, $CHCl_3$). ^1H NMR (300 MHz, CD_3OD): δ = 0.97 (d, *J* = 6.6 Hz, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 1.47–1.60 (m, 2 H), 1.61–1.75 (m, 1 H), 3.37–3.42 (m, 1 H), 3.59 (d, *J* = 2.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 22.5, 23.5, 27.2, 44.2, 58.9, 66.8, 173.2 ppm. IR (film): $\tilde{\nu}$ = 3279 (br), 2955, 2929, 2871, 1753, 1467, 1368 cm^{-1}. HRMS: calcd. for $C_7H_{15}N_2O$ 143.1184; found 143.1178.

(2*R*,3*R*)-2,3-Diamino-5-methylhexanoic Acid (17): A solution of *trans*-(3*R*,4*R*)-**16** (43 mg, 0.3 mmol) in 6 N HCl (1.2 mL) was stirred at room temp. for 4 h. The solvent was then removed to give crude (2*R*,3*R*)-2,3-diamino-5-methylhexanoic acid hydrochloride, which was used in the next step without further purification. ^1H NMR (300 MHz, CD_3OD): δ = 0.99 (d, *J* = 6.3 Hz, 3 H), 1.03 (d, *J* = 6.3 Hz, 3 H), 1.52–1.64 (m, 1 H), 1.76–1.87 (m, 2 H), 3.98–4.03 (m, 1 H), 4.48 (dd, *J* = 3.0, 1.2 Hz, 1 H) ppm. HRMS: calcd. for $C_7H_{17}N_2O_2$ 161.1290; found 161.1279. Treatment of crude hydrochloride with acid resin DOWEX 50WX8 gave 48 mg (quant.) of (2*R*,3*R*)-**17** as a white solid; m.p. 180–182 °C; $[\alpha]_D^{22}$ = +22.0 (*c* = 1.0, CH_3OH). ^1H NMR (300 MHz, CD_3OD): δ = 0.94 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 1.41–1.45 (m, 2 H), 1.71–1.80 (m, 1 H), 3.33–3.38 (m, 1 H), 3.42–3.43 (m, 1 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 21.8, 23.9, 25.4, 40.8, 52.4, 59.2, 175.8 ppm. IR (film): $\tilde{\nu}$ = 3610–3140 (br), 2954, 1640 cm^{-1}. HRMS: calcd. for $C_7H_{17}N_2O_2$ 161.1290; found 161.1292.

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra for new compounds.

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[1] a) W. Dürkheimer, J. Blumbach, R. Lattrell, K. H. Scheunemann, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 180–202; b) R. B. Morin, M. Gorman (Eds.), *Chemistry and Biology of β-lactam Antibiotics*, Academic Press, New York, **1982**, vols. 1–3; c) S. Coulton, E. Hunt in *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products* (Ed.: G. Lukacs), Springer, Berlin, **1993**, vol. 2; d) G. Burton, N. F. Osborne, M. J. Pearson, R. Southgate in *Burger's Medicinal Chemistry and Drug Discovery* (Ed.: M. W. Wolff), Wiley, New York, **1997**, vol. 4, chapter 52.

[2] A. Fleming, *Br. J. Exp. Path.* **1929**, *10*, 226–236.

[3] E. P. Abraham, E. Chain, W. Baker, R. Robinson, *PEN Report No 103*, **1943**.

[4] G. G. F. Newton, E. P. Abraham, *Biochem. J.* **1956**, *62*, 651–658.

[5] a) G. I. Georg (Ed.), *The Organic Chemistry of β-Lactams*, VCH, New York, **1993**; b) *Recent Aspects of the Chemistry of β-Lactams-II*, M. J. Miller (Ed.), Tetrahedron Symposia-in-Print 80, *Tetrahedron* **2000**, *56*, 5553–5742.

[6] a) T. M. Haley, S. J. Angier, A. D. Borthwick, R. Singh, R. G. Micetich, *Drugs* **2000**, *3*, 512–517; b) O. A. Mascaretti, C. E. Boschetti, G. O. Danelon, E. G. Meta, O. A. Roveri, *Curr. Med. Chem.* **1995**, *1*, 441–470.

[7] a) P. E. Finke, S. K. Shah, D. S. Fletcher, B. M. Ashe, K. A. Brause, G. O. Chandler, P. S. Dellea, K. M. Hand, A. L. Maycock, D. G. Osinga, D. J. Underwood, H. Weston, P. Davis, J. B. Doherty, *J. Med. Chem.* **1995**, *38*, 2449–2462; b) J. D. Buynack, A. S. Rao, G. P. Fod, C. Carver, G. Adam, B. Geng, B. Bachmann, S. Shobassy, S. Lackey, *J. Med. Chem.* **1997**, *40*, 3423–3433.

[8] a) W. W. Ogilvie, C. Yoakin, F. Do, B. Hache, L. Lagace, J. Naud, J. A. ÓMeara, R. Deziel, *Bioorg. Med. Chem.* **1999**, *7*, 1521–1531; b) A. D. Borthwick, G. Weingarten, T. M. Haley, M. Tomaszewski, W. Wang, Z. Hu, J. Bedard, H. Jin, L. Yuen, T. S. Mansour, *Bioorg. Med. Chem. Lett.* **1988**, *8*, 365–370; c) P. R. Bonneau, F. Hasani, C. Plouffe, E. Malenfant, S. R. LaPlante, I. Guse, W. W. Ogilvie, R. Plante, W. C. Davidson, J. L. Hopkins, M. M. Morelock, M. G. Cordingley, R. Deziel, *J. Am. Chem. Soc.* **1999**, *121*, 2965–2973.

[9] W. T. Han, A. K. Trehan, J. J. K. Write, M. E. Federico, S. M. Seiller, N. A. Meanwell, *Bioorg. Med. Chem.* **1995**, *3*, 1123–1143.

[10] R. M. Adlington, J. E. Baldwin, B. Chen, S. L. Cooper, W. McCoull, G. J. Pritchard, T. J. Howe, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2037–2040.

[11] a) D. A. Burnett, *Tetrahedron Lett.* **1994**, *35*, 7339–7342; b) W. D. Vaccaro, H. R. Davis, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 313–318; c) S. B. Rosenblum, T. Huynh, A. Afonso, H. R. Davis Jr, N. Yumibe, J. W. Clader, D. A. Burnett, *J. Med. Chem.* **1998**, *41*, 973–980; d) J. W. Clader, D. A. Burnett, M. A. Caplen, M. S. Domalski, S. Dugar, W. Vaccaro, R. Sher, M. E. Browne, H. Zhao, R. E. Burrier, B. Salisbury, H. R. Davis, *J. Med. Chem.* **1996**, *39*, 3684–3693.

[12] X. Quian, B. Zheng, B. Burke, M. T. Saindane, D. R. Kronenthal, *J. Org. Chem.* **2002**, *67*, 3595–3600.

[13] I. Banik, F. F. Becker, B. K. Banik, *J. Med. Chem.* **2003**, *46*, 12–15.

[14] a) C. Palomo, J. M. Aizpurua, A. Benito, J. I. Miranda, R. M. Fratila, C. Matute, M. Domercq, F. Gago, S. Martin-Santamaria, A. Linden, *J. Am. Chem. Soc.* **2003**, *125*, 16243–16260; b) C. Palomo, J. M. Aizpurua, I. Ganboa, A. Benito, L. Cuerdo, R. M. Fratila, A. Jimenez, I. Loinaz, J. I. Miranda, K. R. Pytlewska, A. Micle, A. Linden, *Org. Lett.* **2004**, *6*, 4443–4446.

[15] a) I. Ojima, F. Delaloge, *Chem. Soc. Rev.* **1997**, *26*, 377–386; b) C. Palomo, J. M. Aizpurua, I. Ganboa in *Enantioselective Synthesis of β-Amino acids* (Ed.: E. Juaristi), Wiley-VCH, New York, **1997**, chapter 14, pp. 279–372; c) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Synlett* **2001**, 1813–1826.

[16] a) A. Imada, K. Kitano, K. Kintaka, M. Muroi, M. Asai, *Nature* **1981**, *289*, 590–591; b) R. B. Sykes, C. M. Cimarusti, D. P. Bonner, K. Bush, D. M. Floyd, N. H. Georgopadakou, W. H. Koster, W. C. Liu, W. L. Parker, P. A. Principe, M. L. Rathnum, W. A. Slusarchick, W. H. Trejo, T. S. Wells, *Nature* **1981**, *291*, 489–491.

[17] A. Viso, R. Fernández de la Pradilla, A. García, A. Flores, *Chem. Rev.* **2005**, *105*, 3167–3196.

[18] For a review, see: R. J. Ternansky, J. M. Morin Jr, in *The Organic Chemistry of β-Lactams* (Ed.: G. I. Georg), VCH, New York, **1993**, pp. 257–293.

[19] a) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, D. Ferraris, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 6626–6635; b) B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 1578–1579.

[20] H. Staudinger, *Justus Liebigs Ann. Chem.* **1907**, *356*, 51–123.

[21] T. Storz, B. Bernet, A. Vasella, *Helv. Chim. Acta* **1999**, *82*, 2380–2412.

[22] G. Moyna, H. J. Williams, A. I. Scott, *Synth. Commun.* **1997**, *27*, 1561–1567.

[23] a) T. Fukuyama, R. K. Frank, C. F. Jewell Jr, *J. Am. Chem. Soc.* **1980**, *102*, 2122–2123; b) D. R. Wagle, C. Garai, J. Chiang, M. G. Monteleone, B. E. Kurys, T. W. Strohmeyer, V. R. Hegde, M. S. Manhas, A. K. Bose, *J. Org. Chem.* **1988**, *53*, 4227–4236; c) A. K. Bose, M. S. Manhas, J. M. Van der Veen, S. S. Bari, D. R. Wagle, *Tetrahedron* **1992**, *48*, 4831–4844.

[24] a) G. I. Georg, V. T. Ravikumar in *The Organic Chemistry of β-Lactams* (Ed.: G. I. Georg), VCH, New York, **1993**, chapter 6, pp. 295–368; b) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Eur. J. Org. Chem.* **1999**, 3223–3235.

[25] a) C. Palomo, J. M. Aizpurua, A. Benito, R. Galarza, U. K. Khamrai, J. Vázquez, B. de Pascual-Teresa, P. M. Nieto, A. Linden, *Angew. Chem. Int. Ed.* **1999**, *38*, 3056–3058; b) C. Palomo, J. M. Aizpurua, R. Galarza, A. Benito, U. K. Khamrai, U. Eikeseth, A. Linden, *Tetrahedron* **2000**, *56*, 5563–5570.

[26] C. Palomo, J. M. Aizpurua, M. Legido, A. Mielgo, R. Galarza, *Chem. Eur. J.* **1997**, *3*, 1432–1441.

[27] For reviews, see: a) R. Fernández, J. M. Lassaletta, *Synlett* **2000**, 1228–1240; b) R. Brehme, D. Enders, R. Fernández, J. M. Lassaletta, *Eur. J. Org. Chem.* **2007**, 5629–5660.

[28] R. Fernández, A. Ferrete, J. M. Lassaletta, J. M. Llera, A. Monge, *Angew. Chem. Int. Ed.* **2000**, *39*, 2893–2897.

[29] a) R. Fernández, A. Ferrete, J. M. Lassaletta, J. M. Llera, E. Martín-Zamora, *Angew. Chem. Int. Ed.* **2002**, *41*, 831–833; b) E. Martín-Zamora, A. Ferrete, J. M. Llera, J. M. Muñoz, R. R. Pappalardo, R. Fernández, J. M. Lassaletta, *Chem. Eur. J.* **2004**, *10*, 6111–6129.

[30] Previous communication: E. Díez, R. Fernández, E. Marqués-López, E. Martín-Zamora, J. M. Lassaletta, *Org. Lett.* **2004**, *6*, 2749–2752.

[31] For instance, pure *cis*-(3*R*,4*R*)-**4f** was heated at 80 °C under the reaction conditions (6 equiv. of **1**, 12 equiv. of *i*Pr_2EtN, and 6.5 equiv. of 2-chloro-1-methylpyridinium iodide in toluene). After 24 h no traces of *trans*-**4f** were observed.

[32] W. T. Brady, Y. Q. Gu, *J. Org. Chem.* **1989**, *54*, 2838–2842.

[33] a) W. Kirmse, N. G. Rondan, K. N. Houk, *J. Am. Chem. Soc.* **1984**, *106*, 7989–7991; b) N. G. Rondan, K. N. Houk, *J. Am. Chem. Soc.* **1985**, *107*, 2099–2111; c) R. López, T. L. Sordo, J. A. Sordo, J. González, *J. Org. Chem.* **1993**, *58*, 7036–7037; d) R. López, D. Suárez, M. F. Ruiz-López, J. A. Sordo, T. L. Sordo, *J. Chem. Soc., Chem. Commun.* **1995**, 1677–1678.

[34] The stereochemistry of the Staudinger reaction has been correlated with steric effects: G. I. Georg, P. He, J. Kant, Z. J. Wu, *J. Org. Chem.* **1993**, *58*, 5771–5778. See also ref.[24a]

[35] a) L. Jiao, Y. Liang, J. Xu, *J. Am. Chem. Soc.* **2006**, *128*, 6060–6069; b) Y. Wang, Y. Liang, L. Jiao, D.-M. Du, J. Xu, *J. Org. Chem.* **2006**, *71*, 6983–6990.

[36] a) A. K. Bose, G. Spiegelman, M. S. Manhas, *Tetrahedron Lett.* **1971**, *12*, 3167–3170; b) A. Arrieta, B. Lecea, F. P. Cossio, *J. Org. Chem.* **1998**, *63*, 5869–5876; c) L. S. Hegedus, J. Montgomery, Y. Narukawa, D. C. Snustad, *J. Am. Chem. Soc.* **1991**, *113*, 5784–5791.

[37] For a recent article on the effect of temperature on the stereoselectivity of the Staudinger reaction, see: B. Li, Y. Wang, D.-M. Du, J. Xu, *J. Org. Chem.* **2007**, *72*, 990–997.

[38] R. Fernández, A. Ferrete, J. M. Llera, A. Magriz, E. Martín-Zamora, E. Díez, J. M. Lassaletta, *Chem. Eur. J.* **2004**, *10*, 737–745.

[39] When hydrogenation was carried out using MeOH as the solvent, the corresponding 1-(dimethylamino) derivative was the main product isolated.

[40] Compound (3*R*,4*R*)-**13** gave $[\alpha]_D^{22}$ = +59.0 (*c* = 1.85, CH_3OH). Literature value for (3*S*,4*S*)-**13**: $[\alpha]_D$ = –64.2 (*c* = 0.85, CH_3OH): L. S. Hegedus, R. Imwinkelried, M. Alari-Sargent, D. Dvorak, Y. Satoh, *J. Am. Chem. Soc.* **1990**, *112*, 1109–1117.

[41] Compound (3*R*,4*R*)-**14** gave $[\alpha]_D^{25}$ = –7.4 (*c* = 1, $CHCl_3$). Literature value for (3*S*,4*S*)-**14**: $[\alpha]_D$ = +8.6 (*c* = 0.9, $CHCl_3$): D. A. Evans, E. B. Sjogren, *Tetrahedron Lett.* **1985**, *26*, 3783–3786.

[42] Compound (3*R*,4*S*)-**15** gave $[\alpha]_D^{25}$ = –56.5 (*c* = 1.1, CH_2Cl_2). Literature value for (3*S*,4*R*)-**15**: $[\alpha]_D$ = +62.1 (*c* = 1, CH_2Cl_2): C. Palomo, I. Ganboa, A. Kot, L. Dembkowski, *J. Org. Chem.* **1998**, *63*, 6398–6400.

[43] T. Kawabata, T. Minami, T. Hiyama, *J. Org. Chem.* **1992**, *57*, 1864–1873.

[44] R. C. Thomas, *Tetrahedron Lett.* **1989**, *30*, 5239–5242.

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