Studies on Stereoselective [2+2] Cycloadditions between N,N-Dialkylhydrazones and Ketenes

Eloísa Martín-Zamora,[b] Ana Ferrete,[b] José M. Llera,[c] Jesús M. Muñoz,[b] Rafael R. Pappalardo,[d] Rosario Fernández,*[b] and José M. Lassaletta*[a]

Abstract: Staudinger-like cycloadditions between chiral, non-racemic N,N-dialkylhydrazones **1** and functionalized ketenes constitute an efficient methodology for the stereoselective construction of the β-lactam ring. The potential for fine tuning of the dialkylamino auxiliary structure, the availability of a high-yielding deprotection method for the release of the free azetidinones, and the high thermal and chemical stability of hydrazones as N-dialkylamino imines are highlighted as the key elements for the success of the strategy. This last aspect is of particular importance concerning generality: even hydrazones from easily enolizable aldehydes or from formaldehyde reacted to afford the corresponding cycloadducts with high chemical and stereochemical yields. The syntheses of the β-amino-α-hydroxyacids (2*R*,3*S*)-phenylisoserine (**42**) and (2*R*,3*S*)-norstatin (**45**) were accomplished as illustrative examples of the synthetic utility of this procedure. A model system for the cycloaddition of **g** series auxiliaries was studied by ab initio computational methods. The collected results support a two-step mechanism through zwitterionic intermediates, and explain the observed absolute and relative stereochemistry in terms of the preferred *outward* cycloaddition to the *Re* face of the hydrazone.

Keywords: [2+2] cycloadditions · β-lactams · asymmetric synthesis · hydrazones · synthetic methods

Introduction

Thanks to their high efficacy and extremely safe toxicological profiles, β-lactam antibiotics have for over 60 years been crucial drugs in the war against infectious diseases, being the most widely employed type of antibacterial agents and thus constituting one of the major cornerstones in medicinal chemistry.[1] Since the discovery[2] and structural elucidation of the first isolated members of this family of antibiotics (penicillin G[3] and cephalosporin C[4]), synthetic chemists have intensively investigated the development of methodologies for the construction of the β-lactam skeleton.[5] This activity has sustained its interest because of the constant need for new drugs displaying broader antibacterial activity and/or different biological profiles, while the indiscriminate and massive use of classic antibiotics (both in humans and in livestock) now necessitates the preparation of new β-lactam antibiotics to combat bacteria that have built up resistance against most traditional compounds.

Apart from their clinical use as antibacterial agents, recent reports on the use of β-lactams (especially non-natural ones) for other purposes are also gaining attention. Some of the most notable advances deal with the development of inhibitors, such as those of serine protease,[6] of human leukocyte elastase,[7] of cytomegalovirus protease,[8] of thrombin,[9] of prostate-specific antigen,[10] of cholesterol absorption,[11] and of tryptase.[12] Some β-lactams have also shown anti-cancer activity,[13] and recent studies have demonstrated the utility of synthetic β-lactams as key structures for the synthesis of conformationally restricted peptidomimetics of biological significance.[14] In addition to their importance as bioactive compounds, β-lactams can also be viewed as protected β-amino acids, and enantiopure derivatives have hence been used as chiral building blocks in synthetic organic chemistry.[15]

[a] Dr. J. M. Lassaletta
Instituto de Investigaciones Químicas (CSIC-US)
c/Americo Vespucio s/n, Isla de la Cartuja
41092 Sevilla (Spain)
Fax: (+34) 95-446-0565
E-mail: jmlassa@iiq.csic.es

[b] Dr. E. Martín-Zamora, Dr. A. Ferrete, J. M. Muñoz, Dr. R. Fernández
Dpto. de Química Orgánica
Universidad de Sevilla (Spain)

[c] Dr. J. M. Llera
Dpto. de Química Orgánica y Farmacéutica
Universidad de Sevilla (Spain)

[d] Dr. R. R. Pappalardo
Dpto. de Química Física
Universidad de Sevilla (Spain)

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Among the available methods for the stereocontrolled synthesis of the azetidinone skeleton and their open-chain β-amino acid analogues, catalytic enantioselective approaches such as the enolate–imine[16] and silyl ketene acetal–imine[17] condensations, the Kinugasa reaction,[18] and the [2+2] ketene–imine cycloaddition[19] have recently been described for some derivatives. This last procedure, also known as the Staudinger reaction,[20] is one of the most widely used strategies, due to its simplicity and the availability of the starting materials, and many approaches based on the introduction of chiral auxiliaries in the ketene or in the imine component in order to carry out cycloadditions in a stereoselective way have also been examined.[21] These methodologies, however, in general suffer some limitations, mainly imposed by the poor stabilities of the required imines. With very few exceptions,[22] enolizable aldimines cannot be used in this type of cycloaddition because of their low thermal stabilities and competitive deprotonation by the base required for the generation of the ketene in situ. Formaldimines constitute a second type of unstable imines, due in this case to their tendency to tri- and oligomerize under the conditions used in the Staudinger cycloaddition.[23,24] The particular case of 4-unsubstituted β-lactams, however, deserves particular attention due to the presence of such moieties in nocardicins, as well as in other bioactive compounds such as tabtoxin[25] and the pachystermines,[26] and so indirect, longer routes to these compounds have been developed.[27]

During the last few years, our research group has been investigating the chemical behavior of aldehyde N,N-dialkylhydrazones and their use in asymmetric synthesis in several types of reactions.[28] During these studies, we have regularly observed high stability of such hydrazones even at high temperatures and in the presence of bases and some Lewis acids. The higher stability of hydrazones in relation to imines is most probably due to conjugation between the N-1 lone electron pair and the C=N double bond. Thanks to this, reaction conditions (temperature, presence of acids or bases, etc.) usually incompatible with simple imines can be successfully used with hydrazones, including aliphatic enolizable ones or those derived from formaldehyde. Additionally, the availability of several hydrazones containing tunable chiral auxiliaries prompted us to explore the usefulness of these compounds as imine components in Staudinger-like [2+2] cycloaddition reactions with functionalized ketenes.[29] Here we wish to report the results obtained on the basis of this strategy, together with a theoretical study providing an explanation for the high inductions achieved with the simplest auxiliary and for the observed absolute and relative configurations.

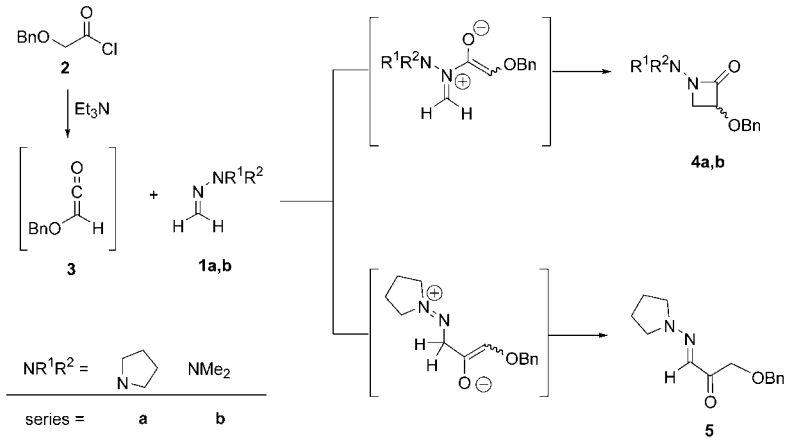
Abstract in Spanish: *La reacción de cicloadición [2+2] de tipo Staudinger entre cetenas funcionalizadas y las hidrazonas quirales **1** constituye un método eficiente para la construcción estereoselectiva del anillo de azetidinona. La modulación de la estructura del grupo dialquilamino empleado como auxiliar, la disponibilidad de un procedimiento eficiente para la desprotección de las β-lactamas libres y la alta estabilidad química y térmica de las hidrazonas como N-dialquilamino iminas son los puntos clave para el éxito de la estrategia. Este último aspecto es de particular importancia por su implicación en la generalidad del método: hidrazonas derivadas de aldehídos fácilmente enolizables o incluso las derivadas de formaldehído reaccionan para dar lugar a los correspondientes cicloaductos con excelentes rendimientos químicos y estereoquímicos. La síntesis de los β-amino-α-hidroxiácidos (2R,3S)-fenilisoserina (**42**) y (2R,3S)-norestatina (**45**) se llevaron a cabo como ejemplos ilustrativos del potencial sintético del método. Estudios computacionales ab initio realizados sobre una reacción modelo basada en los auxiliares de la serie **g** sugieren un mecanismo en dos pasos a través de intermedios zwitteriónicos. Los resultados obtenidos explican la estereoquímica absoluta y relativa, así como el alto grado de inducción observado para estos auxiliares, por la preferencia de la aproximación "outward" de la cetena sobre la cara Re de la hidrazona.*

Results and Discussion

Cycloadditions between formaldehyde N,N-dialkylhydrazones and alkoxy- and aminoketenes: Preliminary reactivity experiments were performed with a model system consisting of benzyloxyketene (**3**; formed in situ from benzyloxyacetyl chloride (**2**) and triethylamine as the base) and 1-(methyleneamino)pyrrolidine (**1a**;[30] Scheme 1). The results collected initially were discouraging: use of chloroform, THF, or Et_2O under a variety of conditions (several temperatures; 1.4 to 2.5 equivalents of triethylamine) resulted in the formation of complex mixtures in which 1-benzyloxy-3-pyrrolidin-1-ylimino)-propan-2-one (**5**; 1,2-adduct to the ketene carbonyl) was found as the major component along with smaller amounts of the desired cycloadduct **4a**. Indeed, when the reaction between hydrazone **1a** and ketene **3** was carried out in CH_2Cl_2 as the solvent between 0 °C and room temperature, only the 1,2-adduct **5** was isolated, in 31 % chemical yield (Scheme 1). The formation of this compound is most probably due to the nucleophilicity of the azomethine carbon of **1a**,[28] which is apparently able to attack the ketene carbonyl of **3**.

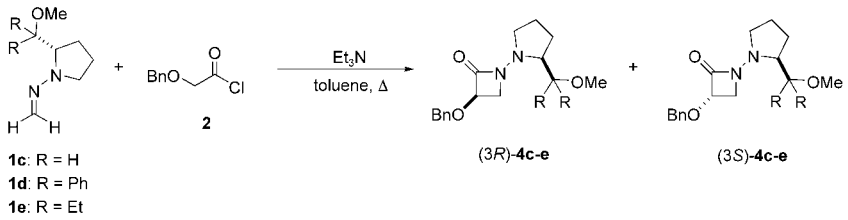
A marked improvement was observed for reactions carried out in toluene at 50 °C; the desired product **4a** could be isolated in 67 % yield without formation of significant amounts of **5**. Additional reactivity experiments were carried out with formaldehyde N,N-dimethylhydrazone **1b**.[31] As would be expected, the lower nucleophilicity of the azomethine carbon of this reagent minimizes the side reaction described above and results in the isolation of the corresponding cycloadduct **4b** in a better yield (84 %) from the reaction carried out in toluene at rt.

Once the desired reactivity was established, we started studies to perform reactions in a stereoselective way. The SAMP-derived formaldehyde hydrazone **1c**[32] (Scheme 2; R = H) exhibited a better reactivity than **1a**, affording cycloadduct **4c** in 80 and 89 % yields at room temperature and 80 °C, respectively, but the observed diastereoselectivities



Scheme 1. Reactions between benzyloxyketene and formaldehyde N,N-dialkylhydrazones: preliminary experiments.

were disappointing in both cases (Table 1, entries 1 and 2). Different approaches to improve the chiral auxiliary were therefore considered.



Scheme 2. Cycloadditions of proline-derived formaldehyde hydrazones **1c–e**.

We first decided to investigate the influence of the steric bulk on other readily available proline-derived hydrazones. Accordingly, hydrazones **1d**[30] (Scheme 2; R = Ph) and **1e**[30] (Scheme 2; R = Et), with bigger (quaternary) residues at position 2, were treated at room temperature with benzyloxyacetyl chloride (**2**) to afford cycloadducts **4d** and **4e** in good yields (85–96%) and with a marked improvement in diastereoselectivity (Table 1, entries 3–6). As in the preceding cases, even better yields and faster reaction times were observed at 80°C, while the diastereoselectivities were influenced very little by this change (entries 4 and 6). The result obtained with hydrazone **1e** was particularly satisfactory, not only because of the better induction observed, but also for the easy chromatographic separation of the (3*R*)- and (3*S*)-**4e** diastereomers, the combination of an excellent 96% chemical yield and a moderate selectivity (*dr* 84:16) thus resulting in the isolation of the pure major isomer (3*R*)-**4e** in 80% yield in a single step (entry 6).

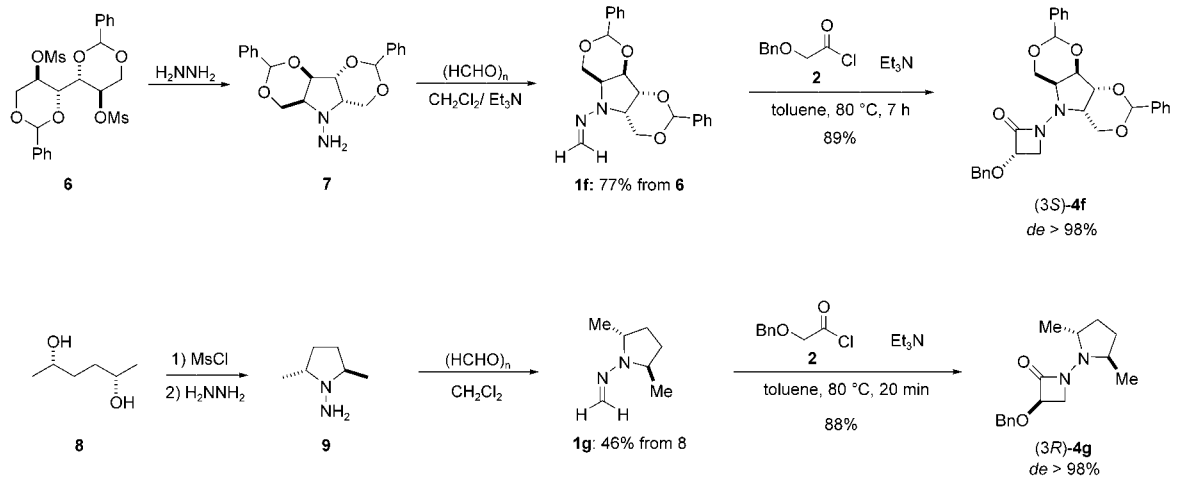
We next investigated the behavior of C_2-symmetric hydrazones, and started experiments with the mannitol-derived reagent **1f**[33] (Scheme 3). The initial interest in this particular compound was the result of several singularities. Firstly, better stereoselectivity could be expected, due to the benefits frequently observed for C_2-symmetric auxiliaries.[34] Secondly, the presence of two neighboring groups at either side (C-2 and C-5) of the C=N double bond, together with the rigidity conferred by the condensed 1,3-dioxane rings, should hinder the planar conformation associated with the competing nucleophilic reactivity of the azomethine carbon.[28] Finally, hydrazone **1f** can be prepared in bulk quantities and in a few steps from inexpensive D-mannitol (Scheme 3). The preparation of the parent hydrazine **7** was carried out by modifying the procedure described in the literature.[35] In this way, the known dimesylate **6**[36] was treated with anhydrous hydrazine to yield **7**, which gave **1f** after condensation with paraformaldehyde in the presence of Et_3N (77% overall yield).

Interestingly, the reaction between hydrazone **1f** and benzyloxyacetyl chloride (**2**) afforded a single isomer **4f**, which was readily isolated in 89% yield under the optimized conditions (toluene, 80°C) found for proline derivatives. This

Table 1. Synthesis of 1-dialkylamino-3-azetidin-2-ones **4c–g**, (*R*)-**14e**, (*S*)-**14e**, and **17e–g**.

Entry	Hydrazone	Ketene	R	*T* [°C]	*t*	Product	Yield [%][a]	*dr*[b]	Conf.[c]
1	**1c**	**3**[d]	H	rt	50 h	**4c**	80	58:42	–[e]
2	**1c**	**3**[d]	H	80	2.5 h	**4c**	89	58:42	–[e]
3	**1d**	**3**[d]	Ph	rt	6 d	**4d**	85	85:15	*R*[e]
4	**1d**	**3**[d]	Ph	80	3.5 h	**4d**	96	81:19	*R*[e]
5	**1e**	**3**[d]	Et	rt	24 h	**4e**	89 (75)	85:15	*R*
6	**1e**	**3**[d]	Et	80	1.5 h	**4e**	96 (80)	84:16	*R*
7	**1f**	**3**[d]	–	80	7 h	**4f**	89	>99:1	*S*
8	**1g**	**3**[d]	–	80	20 min	**4g**	88	>99:1	*R*
9	**1e**	(*R*)-**13**[f]	Et	80	8 h	(*R*)-**14e**	94	>99:1	*R*
10	**1e**	(*S*)-**13**[g]	Et	80	8 h	(*S*)-**14e**	80[h]	98:2	*S*
11	**1e**	**16**[i]	Et	80	23 h	**17e**	93 (76)	82:18	*R*
12	**1f**	**16**[j]	–	60[k]	8 h	**17f**	81	>99:1	*S*
13	**1g**	**16**[i]	–	80	4 h	**17g**	80	>99:1	*R*

[a] Isolated yield after column chromatography. In brackets: yield of isolated, pure major isomer (*de* >98%). [b] Determined by ^{1}H NMR in the crude reaction product. [c] At C3 of major isomer. [d] From 2 equiv **2**. [e] Inseparable mixture of diastereomers. [f] From 1.5 equiv (*R*)-**12**. [g] From 1.5 equiv (*S*)-**12**. [h] Isolated as the pure mayor isomer; the minor isomer was lost during purification. [i] From 2.5 equiv **15**. [j] From 6 equiv **15**. [k] Extensive decomposition of **1f** was observed at 80°C.

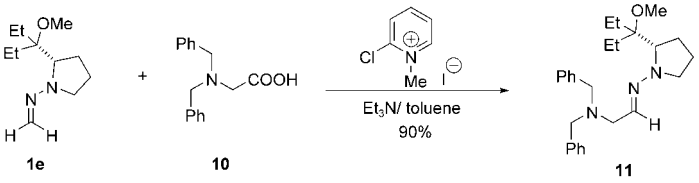


Scheme 3. Cycloadditions of C_2-symmetric hydrazones **1f** and **1g**.

result revealed for the first time the appropriateness of C_2-symmetric auxiliaries for this reaction. As would be expected in view of the relative stereochemistry of **1e** and **1f**, adduct **4f** had the *S* configuration at C-3, opposite to that of the major isomer of **4e**, and so hydrazones **1e** and **1f** in this way complement each other from a stereochemical point of view. However, it should be pointed out that the presumed lack of effective conjugation in **1f** did not result in the expected enhancement of the imine-like reactivity for this compound. In fact, it was found that **1f** is less reactive than proline derivatives towards **3**, as demonstrated by the absence of reactivity at room temperature, and by the longer reaction times (7 h for **1f** versus 1.5 h for **1e**) required for completion at 80 °C.

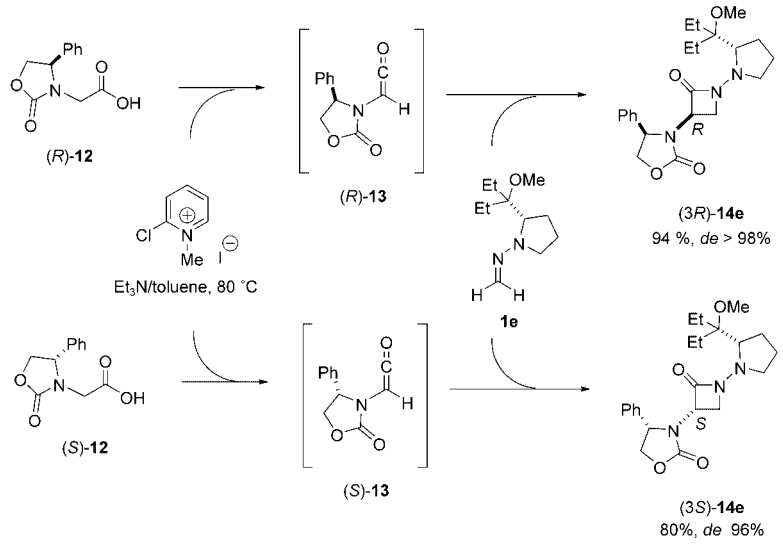
Finally, for reasons fully explained in the next section, the behavior of the C_2-symmetric hydrazone **1g** was also investigated. This product was obtained from the parent hydrazine (2*R*,5*R*)-1-amino-2,5-dimethylpyrrolidine (**9**), which can be efficiently prepared from the commercially available (*S*,*S*)-2,5-hexanediol (**8**).[37] The reaction between hydrazone **1g** and **2** afforded a single isomer **4g**, isolated in 88% chemical yield (Scheme 3, Table 1, entry 8). As in the case of the proline derivatives, **4g** had the *R* configuration at C-3. It should be noted, however, that the enantiomer of **1g** is also easily available, enabling access to the product **4g** with the desired absolute configuration. Additionally, hydrazone **1g** proved to be more reactive than any of the other hydrazones **1a–f** previously employed, as revealed by the shorter reaction times needed for completion (20 min, Table 1, entry 7).

Once the methodology for the preparation of 4-unsubstituted 3-alkoxy-β-lactams had been established, and with account being taken of the fact that many biologically important β-lactam derivatives carry nitrogen functionalities at C-3, cycloadditions between hydrazones **1e–g** and α-aminoketene derivatives were also investigated. A preliminary screening was made with hydrazone **1e** as the reagent and many common combinations of aminoketene precursors (azidoacetyl chloride,[38] phthalimidoacetyl chloride,[39] Dane's salt,[40] azidoacetic acid, and *N*-Boc-glycine) and activators (Et_3N, 2-chloro-*N*-methylpyridinium iodide or tosylate, phenyl dichlorophosphate), under a variety of conditions, but no significant amounts of the desired cycloadducts could be isolated from the complex reaction mixtures. As one exception, though, N,N-dibenzylglycine **10**[41] underwent a clean reaction in the presence of 2-chloro-*N*-methylpyridinium iodide to afford hydrazone **11** as the sole reaction product in 90% yield (Scheme 4).[42]



Scheme 4. Reaction between hydrazone **1e** and dibenzylglycine **10**.

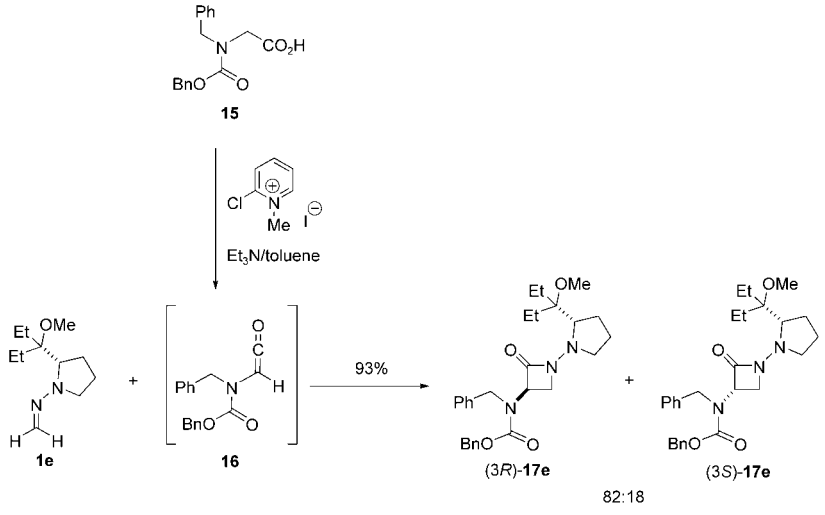
On the other hand, the desired cycloadduct was detected in the reaction between phthaloylglycine and **1e** under different conditions, but was always isolated in low yields and contaminated with unknown impurities. The low thermal stability of the aminoketene generated in the reaction medium (80 °C in toluene) was advanced as a possible explanation for the poor results observed in this case. Since Palomo et al. had described the Staudinger reaction of Evans–Sjogren aminoketene **13** at high temperature,[22] we studied the reactions between hydrazone **1e** and the chiral aminoketenes (*R*)- and (*S*)-**13** (Scheme 5). The best results were obtained by use of the corresponding α-amino acid precursors (*R*)- and (*S*)-**12** and 2-chloro-*N*-methylpyridinium iodide as activating agent[43] for the generation of the aminoketene. A *matched* double induction experiment with (*R*)-**13** and hydrazone **1e** afforded the corresponding adduct (3*R*)-**14e** as a single diastereoisomer in high yield (Table 1, entry 9). The *mismatched* pair formed by hydrazone **1e** and aminoketene (*S*)-**13** gave the corresponding β-lactam in a slower and less clean reaction, although enantiomerically pure (3*S*)-**14e** could be isolated in 80% yield after flash chromatography (entry 10).



Scheme 5. Cycloadditions between hydrazone **1e** and aminoketenes (*S*)- and (*R*)-**13**.

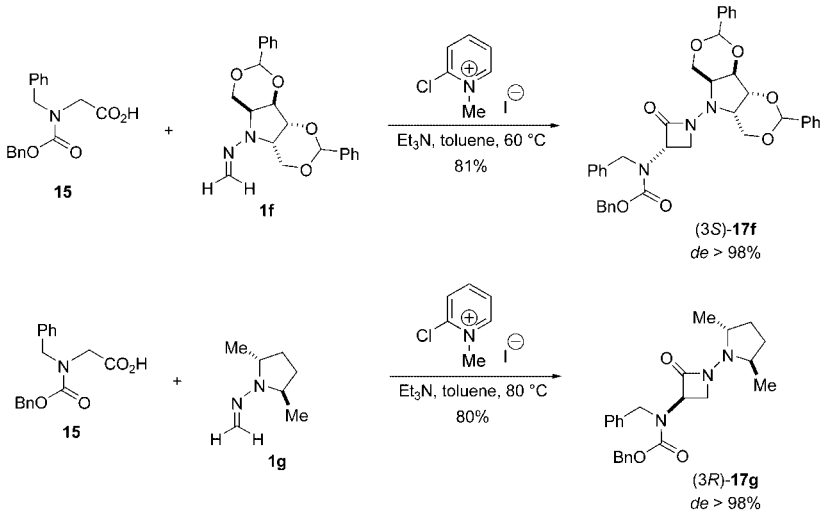
Important conclusions were drawn from these experiments, leading to the design of more efficient strategies:

a) The stability of aminoketene derivatives in the reaction conditions strongly depends on the nature of the substituents on nitrogen. Consequently, we prepared the glycine derivative **15** (Scheme 6), which, carrying the same functionality pattern on nitrogen as **12**, should behave in a similar way. Treatment of aminoketene **16**—generated from **15** under the above conditions—with **1e** afforded adduct **17e** in 93% chemical yield and as an 82:18 mixture of diastereoisomers (Table 1, entry 11). As also observed for the oxygen analogues, the resolving properties of the auxiliary of **1e** allowed easy chromatographic separation of diastereomers (3*R*)- and (3*S*)-**17e**, isolated as pure compounds in 76 and 16% yields, respectively.
b) From the cycloaddition between the *mistmatched* pair of reactants **1e**/(*S*)-**13**, it can be deduced that the induction effected by the chiral oxazolidinone is clearly higher than that of the dialkylamino auxiliary, suggesting a further improvement on the latter. Again, C_2-symmetric dialkylamino groups proved to be more efficient auxiliaries; an almost perfect parallel with the preceding oxygen case was observed in the cycloadditions between hydrazones **1f** and **1g** and aminoketene **16**, with β-lactams **17f** and **17g** also being obtained in good chemical yields and as single diastereoisomers, the two products having opposite configurations at C3 (Scheme 7). Once more, hydrazone **1g** proved to be much more reactive than **1f** and **1e** (Table 1, entries 12 and 13).

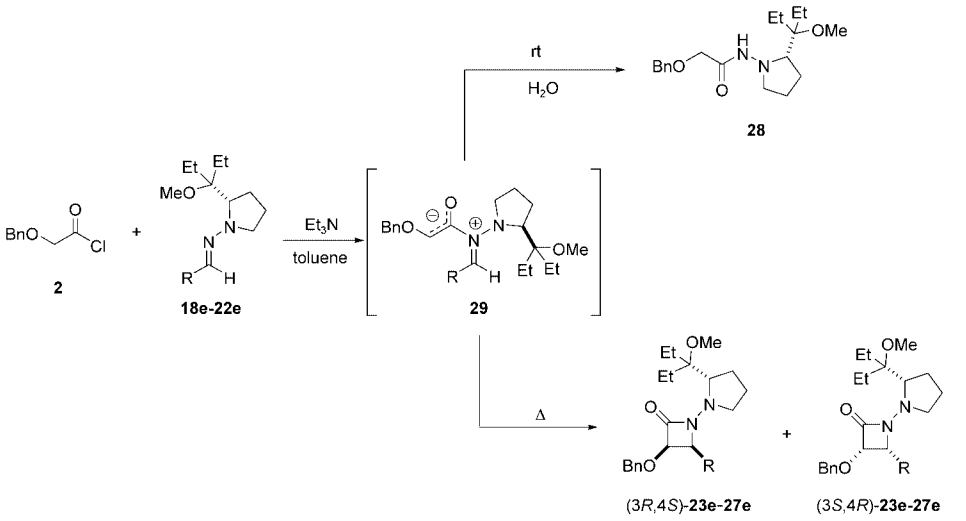


Scheme 6. Cycloaddition between **1e** and aminoketene **16**.

Cycloadditions between higher hydrazones and benzyloxyketene: In view of the above results, we started studies on the extension of the methodology to cycloadditions of higher hydrazones. Since the use of aliphatic, enolizable imines is particularly restricted because of their limited stabilities, we concentrated on cycloadditions of hydrazones derived from easily enolizable aldehydes. In view also of the lack of general approaches for the enantioselective synthesis of 4-alkyl(aryl)-3-hydroxy-β-lactams and their potential as precursors of bioactive β-amino-α-hydroxyacids (isoserines), we focused on [2+2] cycloadditions between chiral aldehyde hydrazones and α-benzyloxyketene **3**.[44] Studies began with treatment of the proline-derived hydrazones **18e**–**22e** with benzyloxyacetyl chloride (**2**), as in the preceding formaldehyde case. Under optimized reaction conditions (toluene, Et_3N, 80 °C for primary substrates, 100 °C for secondary or aromatic hydrazones), the expected cycloadducts **23e**–**27e** were obtained in excellent chemical yields (84–98%) and with moderate to good (3*R*,4*S*)/(3*S*,4*R*) selectivities (Scheme 8, Table 2), with only traces of *trans* isomers being detected in some cases. Nevertheless, the collected results were deemed satisfactory because the major diastereoisomers could be easily separated by flash chromatography in all cases, thus allowing the isolation of the optically pure major *cis* isomers



Scheme 7. Cycloadditions between C_2-symmetric hydrazones **1f** and **1g** and **15**.



Scheme 8. Reactions between **e**-series hydrazones **18e**–**22e** and **2**.

suggests that the higher steric demand in these substrates hinders the conrotatory ring-closure from the zwitterionic species **29**, a generally accepted intermediate in the Staudinger reaction.[45] The formation of **28** can be then explained by assuming hydrolytic CN cleavage of the alkylidene fragment during workup.

The previously collected results from cycloadditions of formaldehyde derivatives made us consider the use of C_2-symmetric auxiliaries in this case as well. Surprisingly, however, treatment of the D-mannitol-derived hydrazone **19f** with **3** afforded only enamine **30** in high yields (>90%) under a variety of conditions (Scheme 9). The observed gap in reactivity between **1f** and **1e** may be associated with their structural differences. The small methylene groups at C2 and C5 in **1f** don't appear to be much more demanding than the bigger side chain at C2 in **1e**. On the other hand, the presence of the two condensed dioxane rings in **1f** strongly restricts the flexibility of the pyrrolidine ring, hindering the ring planarity associated with an effective n–π conjugation. Interestingly, a dramatic difference in the reactivities of **1e** and **1f** had previously been observed in a different context: the nucleophilicity of **1e** allows 1,2-addition to trifluoromethyl ketones, while **1f** fails as reagent in the same reaction.[33] The above considerations suggest that the **f** series hydrazones, due to less effective n–π conjugation, present hybrid chemical behavior lying between proline derivatives and "normal" imines, possessing high chemical stability as in the former, but a tendency to tautomerize closer to the latter. The formation of **30** was consequently attributed to a tautomerization (→**31**)/acylation path (Scheme 9, path a). The initially proposed intramolecular H-transfer[29b] in **32** (Scheme 9, path b) was later ruled out because the calculated geometry of such intermediates (see below) would prevent any significant contribution of n→π conjugative effects, and there would therefore be no explan-

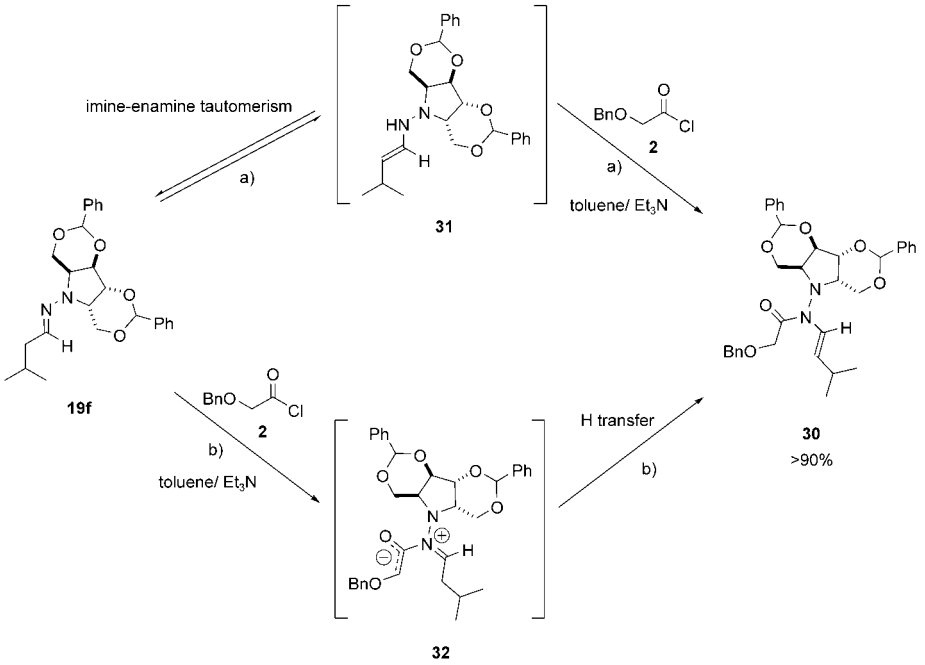
(3*R*,4*S*)-**23e** to (3*R*,4*S*)-**27e** in yields ranging from 70 to 82%. The results collected in Table 2 indicate the generality of the process, as applied both to aromatic and to primary and secondary aliphatic substrates.

Table 2. Synthesis of 4-alkyl(aryl)-1-(N,N-dialkylamino)-3-benzyloxyazetidin-2-ones **23e**–**27e**.

Hydrazone	*T* [°C]	Product	R	Yield [%][a]	*dr*[b,c]	*cis*/*trans*[c]
18e	80	**23e**	*n*-C_5H_{11}	85 (70)	82:18	98:2
19e	80	**24e**	*i*Bu	84 (73)	87:13	98:2
20e	80	**25e**	$Ph(CH_2)_2$	97 (78)	80:20	>99:1
21e	100	**26e**	*i*Pr	90 (82)	91:9	>99:1
22e	100	**27e**	Ph	98 (75)	76:24	>99:1

[a] Isolated yield. Values in parentheses correspond to the pure (*de* 98%) major isomer. [b] (3*R*,4*S*)/(3*S*,4*R*). [c] Determined by ^1H and ^{13}C NMR.

A high reaction temperature (80–100°C) proved to be key for the cycloaddition: interestingly, reactions carried out at room temperature afforded hydrazide **28** as the only identifiable product, in 70–75% yields (Scheme 8). This behavior



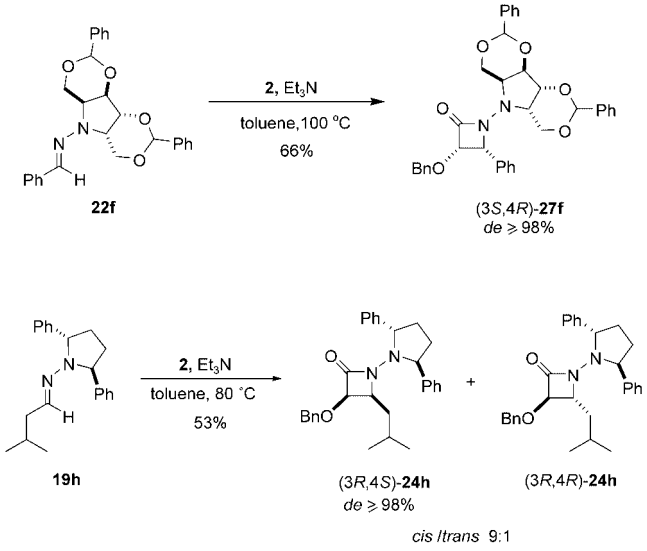
Scheme 9. Reaction between **19f** and **2**.

ation for the observed difference of behavior with proline derivatives.

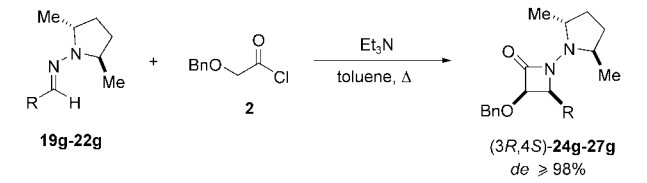
In order to gain further information, the non-enolizable hydrazone **22f** (Scheme 10) was prepared and treated with **2**. Under forcing conditions (100 °C), the desired β-lactam **27f** was formed in a moderate 66 % yield, but with excellent stereoselectivity ($de \geq 98\,\%$). Thus, the introduction of a C_2-symmetric auxiliary seems to be an appropriate strategy, but the lower reactivity of D-mannitol derivatives prevents a better result. The more flexible C_2-symmetric hydrazone **19h** was synthesized and treated with **2** to afford cycloadduct **24h** with complete (3*R*,4*S*)/(3*S*,4*R*) selectivity, supporting the validity of the starting hypothesis, but the yield (53 %) was disappointing and the product was contaminated with ca. 10 % of the undesired *trans* (3*R*,4*R*) diastereomer (Scheme 10). The partial formation of *trans* products and the moderate reactivity of **19h** were now attributed to a higher steric hindrance around the C=N bond.

A final attempt to improve the results obtained with hydrazones **18e**–**22e** was therefore based on the strategy outlined above, but with use of substrates containing the sterically less demanding (2*R*,5*R*)-dimethylpyrrolidine as the auxiliary. As was to be expected, higher reactivities were observed in the reactions between **19g**–**22g** and **2**, which proceeded smoothly to give the corresponding cycloadducts **24g**–**27g** in high yields and, notably, with excellent (3*R*,4*S*)/(3*S*,4*R*) selectivities ($de \geq 98\,\%$) in spite of the low steric demand effected by the small methyl groups at C2 and C5 (Scheme 11, Table 3). In this case, an optimum reaction temperature of 60 °C was applied for treatment of **2** with aliphatic primary hydrazones **19g** and **20g** (Table 3, entries 1 and 4), since significant amounts of *trans* isomers appeared at 80 °C (entries 2 and 5). Interestingly, the high reactivities of **19g**–**22g** allow cycloadditions to be performed even at room temperature (entry 3), in contrast with all other hydrazones tested. Secondary (**21g**) and aromatic (**22g**) hydrazones also reacted smoothly with **2** at optimized temperatures of 80 and 100 °C to give the corresponding adducts **26g** and **27g** in 80 and 96 % yields, respectively (entries 6 and 7).

Deprotection and synthesis of β-amino-α-hydroxyacids: The use of hydrazones as reagents in Staudinger-like cycloadditions to ketenes appears to be a successful strategy in view of two key aspects: 1) the higher stability of hydrazones derived from formaldehyde or aliphatic aldehydes provides an easy route to the 4-unsubstituted and 4-alkylated azetidin-2-one



Scheme 10. Cycloadditions of **22f** and **19h**.



Scheme 11. Cycloadditions of **19g**–**22g**.

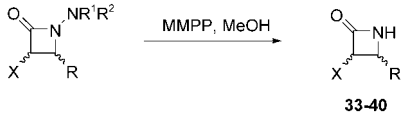
rings, and 2) the potential for tuning of the structure of the chiral dialkylamino auxiliary offers very efficient control over the stereochemical course of the reaction, affording enantiomerically pure compounds in all cases. The success

Table 3. Synthesis of 1-(N,N-dialkylamino)-3-benzyloxyazetidin-2-ones **24g**–**27g**.

Entry	Hydrazone	T [°C]	R	Product	Yield [%][a]	dr[b,c]	*cis*/*trans*[b]
1	**19g**	60	*i*Bu	**24g**	70	>99:1	95:5[d]
2	**19g**	80	*i*Bu	**24g**	91	>99:1	85:15
3	**20g**	rt	$Ph(CH_2)_2$	**25g**	67	>99:1	>99:1
4	**20g**	60	$Ph(CH_2)_2$	**25g**	83	>99:1	>99:1
5	**20g**	80	$Ph(CH_2)_2$	**25g**	91	>99:1	91:9
6	**21g**	80	*i*Pr	**26g**	80	>99:1	>99:1
7	**22g**	100	Ph	**27g**	96	>99:1	>99:1

[a] Yield of isolated product. [b] Determined by ^{13}C and ^{1}H NMR. [c] (3*R*,4*S*)/(3*S*,4*R*) [d] Inseparable mixture. The pure *cis* isomer was obtained after release of the auxiliary (see Table 4, entry 14).

of the whole strategy, however, relies on the availability of an efficient method for the release of the dialkylamino auxiliary to obtain the desired deprotected β-lactams. Unfortunately, the attempted key cleavage of the N–N bonds in adducts **4e** and **4f** by catalytic hydrogenolysis with use of several catalysts [Raney-Ni, Pd/C, and $Pd(OH)_2$/C] or by use of Li/NH_3 under several sets of conditions was unsuccessful. Only large excesses of SmI_2[46] in the presence of HMPA as co-solvent afforded the desired products, but this inconvenient procedure gave only low to moderate yields of product in the investigated 4-unsubstituted cases (**33**: 64–65% from **4e** or **4f**; **34**: 42% from **17e**). We were therefore forced to develop a new procedure for the N–N bond cleavage, which was finally accomplished under oxidative conditions[47] through the use of *N*-oxidation reagents such as *m*-CBPA, magnesium monoperoxyphthalate (MMPP), or Oxone. The best results were observed with methanolic solutions of MMPP, which afforded high yields of product **33**–**40** in all cases (Scheme 12, Table 4). The reactions were performed from single diastereomers except in the case of (3*R*,4*S*)-**24g** (entry 14), which was contaminated with 5% of the inseparable *trans* isomer (Table 3, entry 1). The deprotected product (3*R*,4*S*)-**37**, however, was isolated in 84% yield as the pure *cis* compound; the corresponding deprotected *trans* derivative was presumably removed during chromatographic purification.

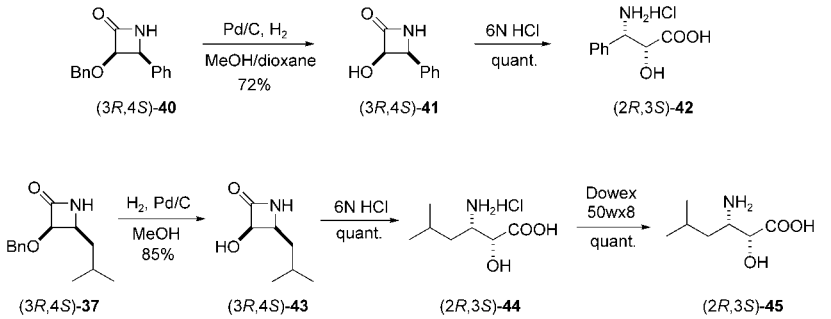


33-40

Scheme 12. Release of the chiral auxiliary: oxidative cleavage of N–N bonds.

Finally, standard transformations from **40** and **37** afforded β-amino-α-hydroxy acids (2*R*,3*S*)-**42**, the side chain of Taxol,[48] and (2*R*,3*S*)-**45**, a component of the renin inhibitor KRI-1230[49] and of antitumoral drug ABT-271[50] (Scheme 13).

Overall, (2*R*,3*S*)-phenylisoserine (**42**) was synthesized in four steps and in 66% and 52% yields from hydrazones



Scheme 13. Synthesis of Taxol side chain (2*R*,3*S*)-**42** and norstatin (2*R*,3*S*)-**45**.

(*R*,*R*)-**22g** and (*S*)-**22e**, respectively, while (2*R*,3*S*)-norstatin **45** was obtained in 50 or 57% overall yields from (*R*,*R*)-**19g** or (*S*)-**19e**, respectively. It is also worth stressing again that the auxiliaries used (**e** and **g** series) are available in both enantiomeric forms.[51] Thus, the same methodology but use of the enantiomeric hydrazones (*S*,*S*)-**19g** or (*R*)-**19e** could be applied to the synthesis of (2*S*,3*R*)-norstatin (*ent*-**45**), a key component of amastatin, a nontoxic inhibitor of aminopeptidase A and leucine aminopeptidase.[52]

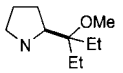
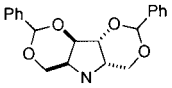
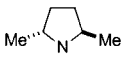
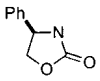
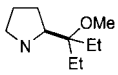
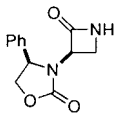
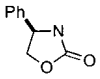
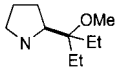
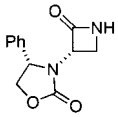
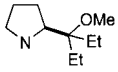
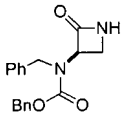
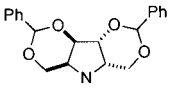
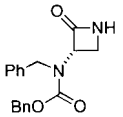
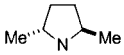
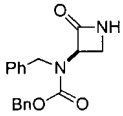
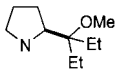
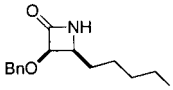
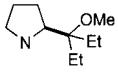
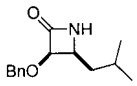
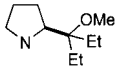
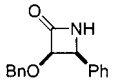
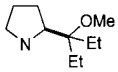
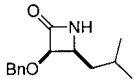
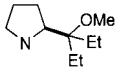
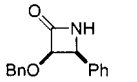
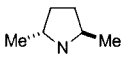
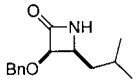
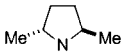
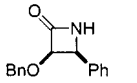
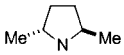
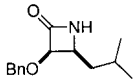
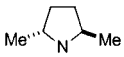
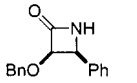
Determination of the absolute configurations: The absolute 3*R* configuration of (3*R*)-**4e** was determined by X-ray diffraction analysis of its derivative (3*R*)-**47**.[29a] The absolute configurations of (3*S*)-**4f** and (3*R*)-**4g** were assigned by chemical correlation according to the transformations shown in Scheme 14.

The absolute configuration of (3*S*)-**17f** was assigned by chemical correlation with the known compound (3*S*)-**48**,[53] while that (3*R*)-**17e** was assigned by comparison of the specific rotations of (3*S*)- and (3*R*)-**35** as shown in Scheme 15.

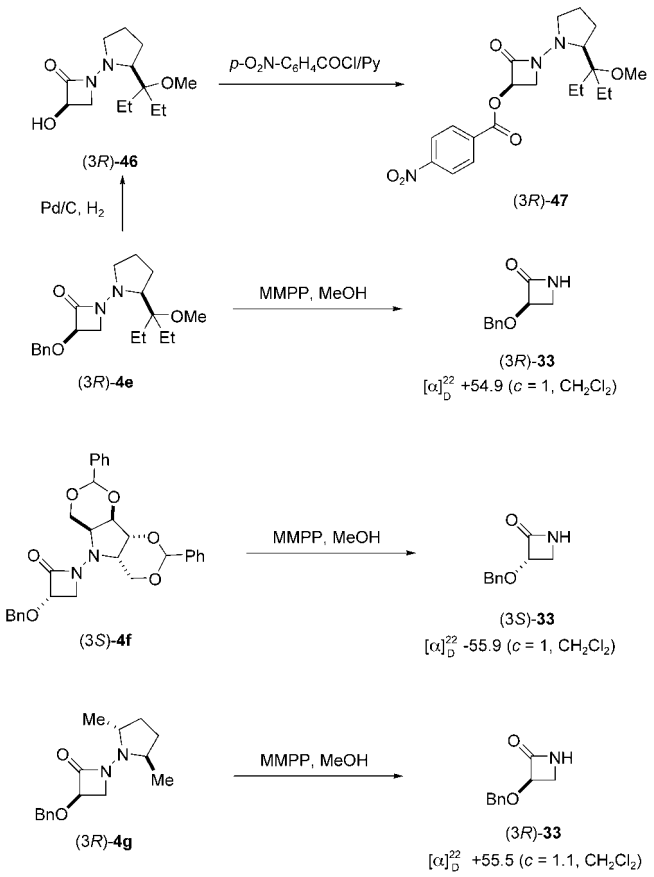
The results of the double induction experiments performed with (*R*)-**13** and (*S*)-**13** are in agreement with the *R* configuration induced by (*S*)-**1e**: the latter forms a *matched* pair with the *R*-inducing ketene (*R*)-**13**,[15a,24,44,54] while the *S* product was formed from the *mismatched* pair (*S*)-**1e**/(*S*)-**13** with predominant *S* induction by the ketene. This last statement was deduced after cleavage of the cycloadducts (3*R*)-**14e** and (3*S*)-**14e**, which afforded the enantiomeric products (3*R*)-**34** and (3*S*)-**34**, respectively (Table 4, entries 4 and 5).

The *cis* stereochemistry was established from the coupling constant $^3J_{H3,H4}$, which can be easily distinguished from that of *trans* isomers.[55] The absolute configuration of (3*R*,4*S*)-**27e** was established by chemical correlation with the known derivative (3*R*,4*S*)-**41**, obtained via (3*R*,4*S*)-**40** (Scheme 13)

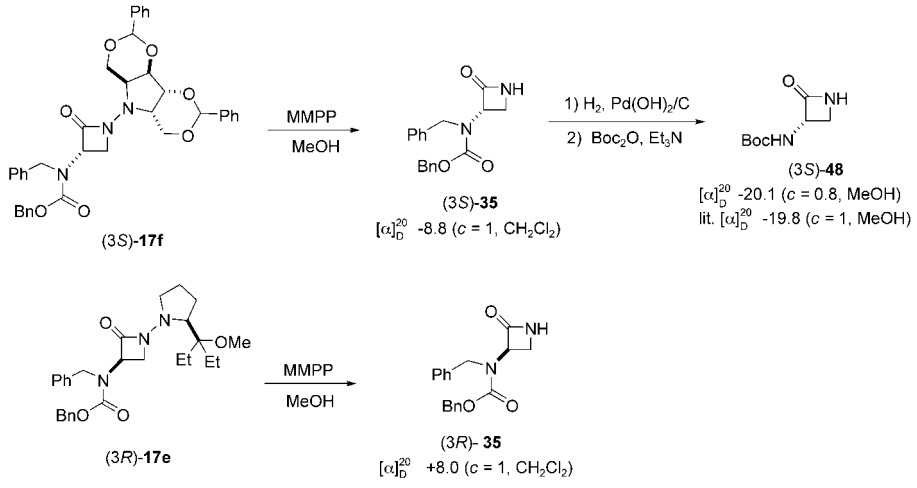
Table 4. Synthesis of azetidin-2-ones **33**–**40** by oxidative N–N bond cleavage of N-dialkylamino-β-lactams.[a]

Entry	Starting compound	X	R	NR^1R^2	*t* [h]	Product	Yield [%][b]
1	(3*R*)-**4e**	OBn	H		1	 (3*R*)-**33**	89
2	(3*S*)-**4f**	OBn	H		6	 (3*S*)-**33**	82
3	(3*R*)-**4g**	OBn	H		2	 (3*R*)-**33**	82
4	(3*R*)-**14e**		H		2.5	 (3*R*)-**34**	75
5	(3*S*)-**14e**		H		1.75	 (3*S*)-**34**	71
6	(3*R*)-**17e**		H		1	 (3*R*)-**35**	83
7	(3*S*)-**17f**		H		6	 (3*S*)-**35**	82
8	(3*R*)-**17g**		H		2	 (3*R*)-**35**	83
9	(3*R*,4*S*)-**23e**	OBn	n-C_5H_{11}		3	 (3*R*,4*S*)-**36**	78
10	(3*R*,4*S*)-**24e**	OBn	*i*Bu		2.5	 (3*R*,4*S*)-**37**	91
11	(3*R*,4*S*)-**25e**	OBn	$Ph(CH_2)_2$		2	 (3*R*,4*S*)-**38**	87
12	(3*R*,4*S*)-**26e**	OBn	*i*Pr		4	 (3*R*,4*S*)-**39**	88
13	(3*R*,4*S*)-**27e**	OBn	Ph		2	 (3*R*,4*S*)-**40**	96
14	(3*R*,4*S*)-**24g**	OBn	*i*Bu		2	 (3*R*,4*S*)-**37**	84[c]
15	(3*R*,4*S*)-**25g**	OBn	$Ph(CH_2)_2$		2	 (3*R*,4*S*)-**38**	84
17	(3*R*,4*S*)-**26g**	OBn	*i*Pr		2	 (3*R*,4*S*)-**39**	91
18	(3*R*,4*S*)-**27g**	OBn	Ph		2	 (3*R*,4*S*)-**40**	95

[a] Substrate/MMPP 1:6. [Substrate] = 0.4 M. [b] Of isolated product after column chromatography. [c] Of pure *cis* isomer.



Scheme 14. Determination of the absolute configurations of (3*R*)-**4e**, (3*S*)-**4f**, and (3*R*)-**4g**.



Scheme 15. Determination of the absolute configurations of (3*S*)-**17f** and (3*R*)-**17e**.

precursors (3*R*,4*S*)-**24e** and (3*R*,4*S*)-**24g** were assigned after the synthesis of (2*R*,3*S*)-norstatin as described above.

Computational studies: Since there was no evident explanation for the almost complete inductions achieved by the use of the rather simple 2,5-dimethylpyrrolidine auxiliary, we decided to perform a computational study in order to understand the stereochemical outcome of the reaction better. Ab initio calculations at the B3LYP6-31G* level were applied to the cycloaddition of acetaldehyde hydrazone **H** and methoxyketene **K** as the model system. In agreement with previous studies on the Staudinger reaction,[45] our results support a two-step mechanism consisting of: i) nucleophilic attack of the imine nitrogen to the ketene carbonyl, leading to a zwitterionic intermediate **ZW** trough a transition state **TS1**, and ii) electrocyclic conrotatory ring-closure via **TS2** to the final product **P**. Four different paths can be considered by combining two relative positions of the methoxy residue of **K** (*outward* or *inward*) and the two diastereomeric faces (*Re*,*Si*) of the C=N bond of **H** (Scheme 16).

The stationary points corresponding to the transition states **TS1** (first step) and **TS2** (second step), the zwitterionic intermediates **ZW**, and the final products **P** were located for the paths described above and fully characterized by computation of the vibrational frequencies. The relative energies calculated for these structures are collected in Table 5.

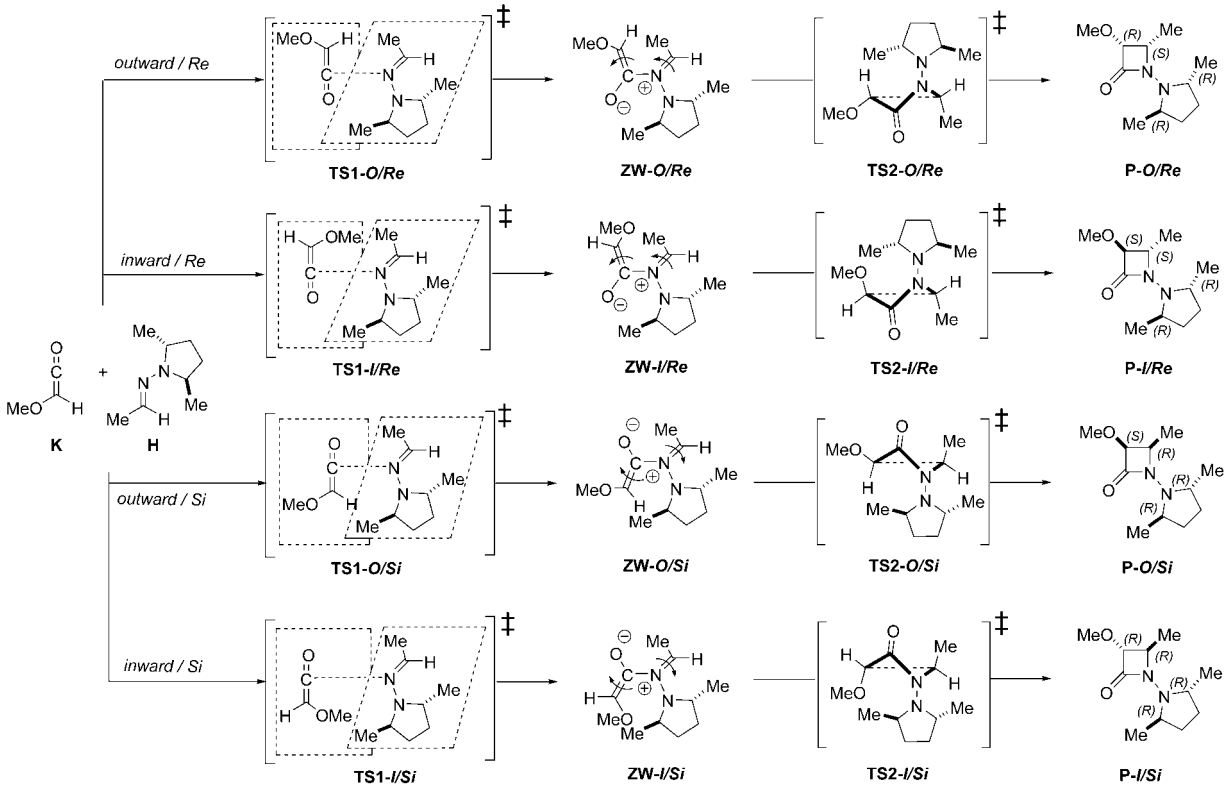
Analysis of these data suggests that, as in related keteneimine systems,[45] the conrotatory ring-closure appears, in general, to be the rate-determining step. A strong preference for the *outward* approaches can be deduced from the different energies of the **TS2** and **ZW** structures. Thus, the calculated energy barriers for *outward* approaches are 5.1 and 6.3 kcal mol^{-1} for the *Re* and *Si* attacks, respectively. In sharp contrast, the barriers corresponding to *inward* approaches are 16.9 and 17.6 kcal mol^{-1}. This tendency is also consistent with previous studies on related cycloadditions with electron-rich ketenes, a fact analyzed in terms of the so-called *torquoelectronic* effect.[57]

In order to explain the preference for the **P-*O*/*Re*** product, it is therefore necessary to com-

($[\alpha]_D^{31}$ = +181.9 (*c* = 1.3, MeOH); lit. $[\alpha]_D$ = 182–193 (MeOH)[56]). Compound (3*R*,4*S*)-**40** ($[\alpha]_D^{25}$ = +97.3 (*c* = 1, DMSO)) was also obtained from (3*R*,4*S*)-**27g**, which therefore had the same absolute configuration as (3*R*,4*S*)-**27e** at C3 and C4. The obtaining of the enantiomer (3*S*,4*R*)-**40** ($[\alpha]_D^{31}$ = −102.4 (*c* = 0.3, DMSO)) from (3*S*,4*R*)-**27f** confirmed the absolute configuration assigned to the latter. Finally, the absolute configurations of (3*R*,4*S*)-**37** and their

Table 5. Relative energies for the stationary points.

Pathway	Relative energies [kcal mol^{-1}]			
	TS1	ZW	TS2	P
outward/*Re*	3.4	3.1	8.2	−36.4
inward/*Re*	3.8	2.2	19.1	−36.5
outward/*Si*	7.7	6.3	12.6	−35.8
inward/*Si*	8.0	5.6	23.2	−32.6



Scheme 16. Possible reaction paths between methoxyketene **K** and acetaldehyde **g** series hydrazone **H** according to a two-step mechanism via zwitterionic intermediates.

pare the calculated relative energies for the stationary points along the *outward*/*Re* and *outward*/*Si* paths (Figure 1). Firstly, the most stable **ZW-*O*/*Re*** intermediate is

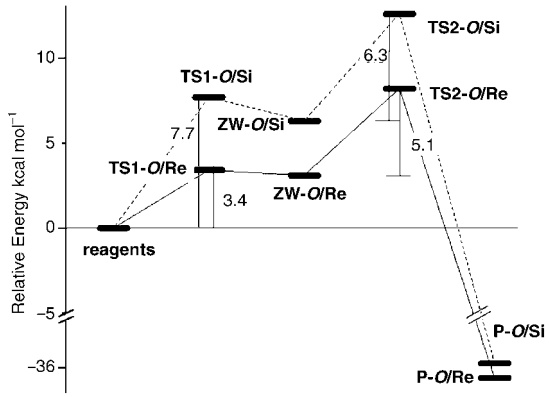


Figure 1. Energy profiles for the *outward*/*Re* and *outward*/*Si* paths.

formed through a less energy-demanding addition step (3.4 kcal mol^{-1} for **TS1-*O*/*Re*** versus 7.7 kcal mol^{-1} for **TS1-*O*/*Si***). Moreover, the second step operates in the same sense: the barrier leading to product **P-*O*/*Re*** through the essentially irreversible ring-closing step is also smaller (5.1 versus 6.3 kcal mol^{-1} for **P-*O*/*Si***).

A careful analysis of the relevant structures shown in Figure 2 suggests a description of the data reported above in terms of two significant interactions:

a) There are CH···O hydrogen bonds that contribute to the stabilization of the proposed structures. However, there is a considerable difference in the number and efficiency of these interactions in the two paths: the *outward*/*Re* transition states **TS1-*O*/*Re*** and **TS2-*O*/*Re*** (as well as the zwitterionic intermediate **ZW-*O*/*Re***) each exhibit two of these hydrogen bonds, while the structures corresponding to the *outward*/*Si* pathway present only the NCH···O bond. The most significant difference appears through comparison of the ring-closing transition states **TS2-*O*/*Re***, with H–O distances of 2.51 and 2.49 Å, and **TS2-*O*/*Si***, which has only a weak CH···O bond with an H–O distance of 2.61 Å.

b) The methyl groups at C2 and C5 in the pyrrolidine ring arrange in almost perfect pseudoequatorial positions in the calculated *outward*/*Re* stationary points. In the *outward*/*Si* transition states and zwitterionic intermediate, however, one of the methyl groups arranges in an almost perfect pseudoaxial position. As a direct consequence, there are considerable steric interactions that should contribute to the higher relative energy calculated for the latter. The short C(Me)–C(ketene carbonyl) distances in **ZW-*O*/*Si*** (3.11 Å) and **TS2-*O*/*Si*** (3.09 Å) are representative examples of this effect.

In summary, a model based on the computational study is proposed. According to this model, the absolute and relative absolute configurations are the result of a favored *outward* cycloaddition involving the *Re* face of the hydrazone. This

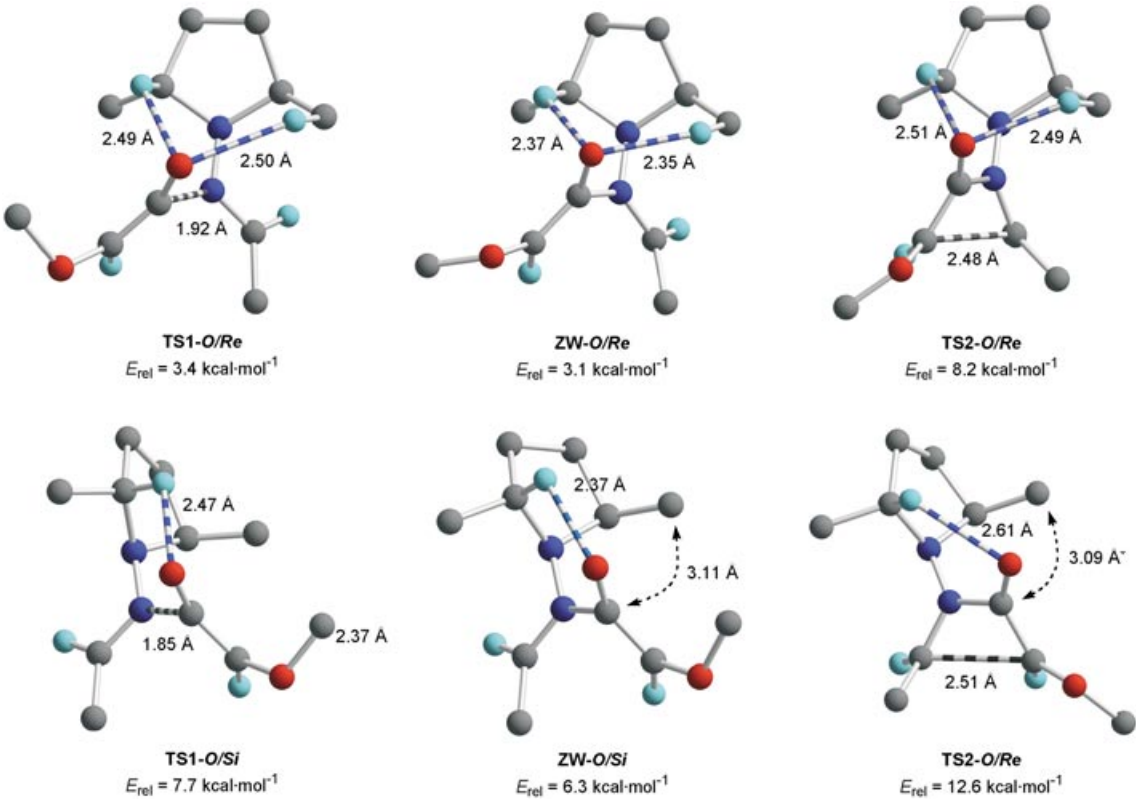


Figure 2. Transition states **TS1** and **TS2** and zwitterionic intermediates **ZW** for the *outward*/*Re* and *outward*/*Si* approaches.

approach is less energy-demanding than that resulting from the attack to the *Si* face of the C=N bond, mainly due to the contribution of stabilizing CH···O hydrogen bonds and the absence of CO–Me repulsive interactions.

Conclusion

The obtained results indicate that chiral N,N-dialkylhydrazones are advantageous reagents for use as imine components in Staudinger [2+2] cycloadditions with functionalized ketenes. The stability of formaldehyde and enolizable substrates gives the method generality, while the potential for fine tuning of the auxiliary offers efficient control over the stereochemical course of the reaction. The method could be applied to the synthesis of bioactive isoserines, which were synthesized in a reduced number of steps thanks to the multiple roles played by the dialkylamino residue. In fact, the optimized 2,5-dimethylpyrrolidine moiety was used simultaneously as stabilizing function, chiral auxiliary, and protecting group.

Experimental Section

General methods: Melting points were determined on a metal block and are uncorrected. Optical rotations were measured at room temperature. FT-IR spectra were recorded on KBr pellets or films. EI-mass spectra were recorded at 70 eV, with use of an ionizing current of 100 mA, an accelerating voltage of 4 kV, and a resolution of 1000 or 10000 (10% valley definition). The reactions were monitored by TLC. Purification of the products was carried out by chromatography (silica gel). The light petroleum ether used had a boiling range of 40–65 °C. All the calculations were performed by use of Gaussian98W[58] with the standard 6-31G** basis set[59] and the B3-LYP[60] method; see Supporting Information for further details.

General procedure for the synthesis of 1-dialkylamino-3-benzyloxyazetidin-2-ones 4a–g: A solution of benzyloxyacetyl chloride (**2**, 2 mmol, 0.33 mL) in toluene (5 mL) was added dropwise to a solution of the hydrazone **1a–g** (1 mmol) and TEA (4 mmol, 0.56 mL) in dry toluene (10 mL). The mixture was heated until consumption of the starting hydrazone and washed with water, and the aqueous layer was extracted with EA (2×15 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (Et_2O/DCM/PE) gave the corresponding 1-(dialkylamino)-3-benzyloxyazetidin-2-ones **4a–g**. Starting materials, reaction times, and characterization data were as follows:

3-Benzyloxy-1-pyrrolidin-1-yl-azetidin-2-one (4a): This compound was prepared from hydrazone **1a**,[30] the reaction being complete after 2.5 h at 50 °C. Flash chromatography (Et_2O/DCM/PE 1:1:2) gave **4a** (165 mg, 67%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.81–1.85 (m, 4H), 2.90–2.96 (m, 4H), 3.27 (dd, J = 1.8, 5.2 Hz, 1H), 3.52 (t, J = 4.9 Hz, 1H), 4.57 (dd, J = 1.8, 4.8 Hz, 1H), 4.64 (d, J = 11.5 Hz, 1H), 4.85 (d, J = 11.5 Hz, 1H), 7.31–7.39 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1 (2C), 45.0, 51.2 (2C), 72.3, 77.3, 128.0, 128.1, 128.4, 136.7, 166.2 ppm; IR (KBr): $\tilde{\nu}$ = 1769, 1458, 1092, 1028 cm^{-1}; MS (EI): m/z (%): 246 (0.3) $[M]^+$, 127 (68), 91 (100), 56 (40); elemental analysis calcd (%) for $C_{14}H_{18}N_2O_2$: C 68.27, H 7.37, N 11.37; found C 68.28, H 7.40, N 11.60.

3-Benzyloxy-1-(dimethylamino)azetidin-2-one (4b): This compound was prepared from hydrazone **1b**, the reaction being complete after 48 h at rt. Flash chromatography (Et_2O/DCM/PE 1:1:1) gave **4b** (185 mg, 84%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.58 (s, 6H), 3.25 (dd, J = 1.9, 5.2 Hz, 1H), 3.50 (td, J = 4.7, 5.2 Hz, 1H), 4.56 (dd, J = 1.9, 4.7 Hz, 1H), 4.65 (d, J = 11.5 Hz, 1H), 4.84 (d, J = 11.5 Hz, 1H), 7.30–7.40 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.1, 44.4, 72.3, 77.6, 128.0, 128.1, 128.4, 136.7, 165.2 ppm; IR (KBr): $\tilde{\nu}$ = 1768, 1458, 1093,

1029 cm^{-1}; MS (EI): *m*/*z* (%): 220 (2) $[M]^+$, 101 (100), 91 (65), 58 (22); elemental analysis calcd (%) for $C_{12}H_{16}N_2O_2$: C 65.43, H 7.32, N 12.72; found C 65.26, H 7.60, N 12.94.

(3*R*)- and (3*S*)-3-Benzyloxy-1-[(2*S*)-2-methoxymethyl-pyrrolidin-1-yl]azetidin-2-one [(3*R*)- and (3*S*)-4c]: These compounds were prepared from hydrazone **1c**, the reaction being complete after 2.5 h at 80 °C. Flash chromatography (Et_2O/DCM/PE 1:1:2→1:1:1) gave **4c** (258 mg, 89 %) as an inseparable mixture of diastereoisomers (3*R*)- and (3*S*)-**4c** (*dr* 58:42). ^{1}H NMR (500 MHz, $CDCl_3$) (3*R*)-**4c**: δ = 1.57–1.64 (m, 1H), 1.75–1.89 (m, 2H), 1.90–1.99 (m, 1H), 2.90 (q, *J* = 7.6 Hz, 1H), 3.10–3.24 (m, 2H), 3.25 (dd, *J* = 1.8, 5.0 Hz, 1H), 3.32 (s, 3H), 3.38–3.48 (m, 2H), 3.56 (t, *J* = 5.0 Hz, 1H), 4.54 (dd, *J* = 1.8, 4.8 Hz, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 4.83 (d, *J* = 11.6 Hz, 1H), 7.29–7.38 ppm (m, 5H); (3*S*)-**4c** δ = 1.57–1.64 (m, 1H), 1.75–1.89 (m, 2H), 1.90–1.99 (m, 1H), 2.90 (q, *J* = 7.6 Hz, 1H), 3.10–3.24 (m, 2H), 3.33–3.35 (m, 1H), 3.34 (s, 3H), 3.38–3.48 (m, 2H), 3.50 (t, *J* = 4.9 Hz, 1H), 4.56 (dd, *J* = 1.9, 4.7 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.83 (d, *J* = 11.6 Hz, 1H), 7.29–7.38 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) (3*R*)-**4c**: δ = 20.9, 26.0, 45.7, 51.8, 59.0, 60.9, 72.1, 75.2, 77.4, 127.9, 128.0, 128.1, 128.4, 137.0, 166.7 ppm; (3*S*)-**4c**: δ = 21.1, 26.1, 46.2, 51.9, 59.1, 61.1, 72.2, 75.0, 77.4, 127.9, 128.0, 128.1, 128.4, 137.0, 166.7 ppm; IR (KBr): $\tilde{\nu}$ = 1768, 1453, 1114, 1027 cm^{-1}; MS (CI): *m*/*z* (%): 291 (80) $[M+H]^+$, 129 (100), 91 (62); elemental analysis calcd (%) for $C_{16}H_{22}N_2O_3$: C 66.18, H 7.64, N 9.65; found C 66.16, H 7.70, N 9.56.

(3*R*)- and (3*S*)-3-Benzyloxy-1-[(2*S*)-2-(methoxydiphenylmethyl-pyrrolidin-1-yl]-azetidin-2-one [(3*R*)- and (3*S*)-4d]: These compounds were prepared from hydrazone **1d**, the reaction being complete after 3.5 h at 80 °C. Flash chromatography (Et_2O/DCM/PE 1:1:4) gave **4d** (424 mg, 96 %) as an inseparable mixture of diastereoisomers (3*R*)- and (3*S*)-**4d** (*dr* 81:19). ^{1}H NMR (500 MHz, $CDCl_3$) (3*R*)-**4d**: δ = 0.21–0.33 (m, 1H), 1.22–1.34 (m, 1H), 1.58–1.65 (m, 1H), 1.93–2.18 (m, 1H), 2.61 (br s, 1H), 2.71–2.81 (m, 1H), 2.79 (s, 3H), 2.89–2.94 (m, 1H), 3.03 (dd, *J* = 1.6, 4.9 Hz, 1H), 4.16 (dd, *J* = 1.6, 4.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.44–4.49 (m, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 7.14–7.56 ppm (m, 15H); (3*S*)-**4d**: δ = 0.21–0.33 (m, 1H), 1.22–1.34 (m, 1H), 1.58–1.65 (m, 1H), 1.93–2.18 (m, 1H), 2.71–2.81 (m, 1H), 2.81 (s, 3H), 2.89–2.94 (m, 2H), 3.29 (t, *J* = 4.9 Hz, 1H), 4.09–4.10 (m, 1H), 4.21 (dd, *J* = 3.5, 10 Hz, 1H), 4.44–4.49 (m, 1H), 4.60–4.71 (m, 1H), 7.14–7.56 ppm (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) (3*R*)-**4d**: δ = 22.7, 27.2, 49.6, 51.7, 54.0, 66.9, 72.1, 77.7, 85.9, 127.1–130.3 (m), 137.1, 138.0, 138.2, 140.0, 140.1, 165.9 ppm; (3*S*)-**4d**: δ = 22.4, 27.0, 47.3, 51.7, 53.2, 66.4, 72.1, 77.7, 85.9, 127.1–130.3 (m), 137.1, 138.0, 138.2, 140.0, 140.1, 165.6 ppm; IR (KBr): $\tilde{\nu}$ = 1762, 1452, 1093, 1038 cm^{-1}; MS (CI): *m*/*z* (%): 443 (5) $[M+H]^+$, 411 (100), 245 (70), 91 (56); elemental analysis calcd (%) for $C_{28}H_{30}N_2O_3$: C 76.00, H 6.83, N 6.33; found C 76.11, H 7.03, N 6.10.

(3*R*)- and (3*S*)-3-Benzyloxy-1-[(2*S*)-2-(1-ethyl-1-methoxypropyl) pyrrolidin-1-yl]azetidin-2-one [(3*R*)- and (3*S*)-4e]: These compounds were prepared from hydrazone **1e**, the reaction being complete after 1.5 h at 80 °C. Flash chromatography (Et_2O/DCM/PE 1:1:3) of the crude oil (*dr* 84:16) allowed separation of both diastereoisomers.

Diastereoisomer (3*R*)-4e: (266 mg, 80 %); $[\alpha]_D^{21}$ = +8.6 (*c* = 1 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83–0.87 (m, 6H), 1.46–1.60 (m, 2H), 1.61–1.69 (m, 2H), 1.70–1.90 (m, 4H), 2.87–2.92 (m, 1H), 3.11–3.15 (m, 1H), 3.26 (s, 3H), 3.26–3.31 (m, 2H), 3.47 (t, *J* = 4.9 Hz, 1H), 4.49 (dd, *J* = 1.8, 4.7 Hz, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.82 (d, *J* = 11.6 Hz, 1H), 7.26–7.34 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.0, 8.4, 23.5, 23.6, 25.6, 26.4, 46.1, 50.3, 54.2, 66.4, 72.2, 77.4, 79.6, 128.0, 128.1, 128.5, 137.2, 165.8 ppm; IR (KBr): $\tilde{\nu}$ = 1762, 1458, 1088, 1030 cm^{-1}; MS (EI): *m*/*z* (%): 346 (3) $[M]^+$, 245 (100), 101 (19), 91 (56); elemental analysis calcd (%) for $C_{2o}H_{30}N_2O_3$: C 69.33, H 8.73, N 8.09; found C 68.99, H 8.44, N 8.10.

Diastereoisomer (3*S*)-4e: (50 mg, 15 %); $[\alpha]_D^{21}$ = −50.9 (*c* = 1.3 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.5 Hz, 6H), 1.23–1.57 (m, 2H), 1.60–1.65 (m, 2H), 1.73–1.86 (m, 4H), 2.90–2.94 (m, 1H), 3.13–3.19 (m, 1H), 3.24–3.25 (m, 1H), 3.25 (s, 3H), 3.49 (t, *J* = 4.9 Hz, 1H), 4.45 (dd, *J* = 1.8, 4.8 Hz, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.80 (d, *J* = 11.6 Hz, 1H), 7.24–7.35 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.9, 8.5, 23.1, 23.6, 25.5, 26.3, 45.8, 50.2, 53.9, 66.3, 72.3, 77.3, 79.6, 128.0, 128.2, 128.5, 137.1, 166.0 ppm; IR (KBr): $\tilde{\nu}$ = 1762, 1458, 1088, 1030 cm^{-1}; MS (EI): *m*/*z* (%): 346 (2) $[M]^+$, 245 (100), 101 (19), 91 (64); elemental analysis calcd (%) for $C_{20}H_{30}N_2O_3$: C 69.33, H 8.73, N 8.09; found C 69.34, H 8.54, N 8.06.

Compound [(3*R*)- and (3*S*)-4f]: This compound was prepared from hydrazone **1f**, the reaction being complete after 7 h at 80 °C. Flash chromatography (Et_2O/PE 2:1) gave (3*S*)-**4f** (460 mg, 89 %) as a single crystalline diastereoisomer (*dr* >99:1). M.p. 77–80 °C; $[\alpha]_D^{21}$ = +88.5 (*c* = 1 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.39 (dd, *J* = 2.1, 5.0 Hz, 1H), 3.68 (br s, 2H), 3.86 (t, *J* = 5.0 Hz, 1H), 4.07 (dd, *J* = 2.6, 13.1 Hz, 2H), 4.23 (d, *J* = 13.1 Hz, 2H), 4.42 (d, *J* = 2.5 Hz, 2H), 4.66 (dd, *J* = 2.1, 4.8 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.87 (d, *J* = 11.6 Hz, 1H), 5.45 (s, 2H), 7.29–7.45 ppm (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 48.7, 57.1 (2C), 65.3, 72.5, 77.2, 78.1 (2C), 99.5 (2C), 126.0–129.1 (m), 136.9, 137.5, 169.2 ppm; IR (KBr): $\tilde{\nu}$ = 1771, 1395, 1111, 1018 cm^{-1}; MS (EI): *m*/*z* (%): 514 (10) $[M]^+$, 261 (40), 105 (100), 91 (83); elemental analysis calcd (%) for $C_{30}H_{30}N_2O_6$: C 70.02, H 5.88, N 5.44; found C 69.82, H 5.86, N 5.46.

(3*R*)-3-Benzyloxy-1-[(2*R*,5*R*)-2,5-dimethyl-pyrrolidin-1-yl]azetidin-2-one (4g): This compound was prepared from hydrazone **1g**, the reaction being complete after 20 min at 80 °C. Flash chromatography (Et_2O/DCM/PE 1:1:3→1:1:2) gave (3*R*)-**4g** (241 mg, 88 %) as a single diastereomer (*dr* >99:1). $[\alpha]_D^{28}$ = +2.1 (*c* = 1 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 6.3 Hz, 6H), 1.32–1.48 (m, 2H), 1.95–2.06 (m, 2H), 3.40–3.44 (m, 2H), 3.54–3.60 (m, 2H), 4.65 (dd, *J* = 2.6, 4.0 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.85 (d, *J* = 11.6 Hz, 1H), 7.32–7.37 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.5 (2C), 30.0 (2C), 51.9 (2C), 56.2, 72.2, 77.4, 128.0, 128.1, 128.5, 137.0, 167.9 ppm; IR (KBr): $\tilde{\nu}$ = 1768, 1458, 1093, 1032 cm^{-1}; MS (EI): *m*/*z* (%): 274 (11) $[M]^+$, 155 (32), 91 (100), 84 (47); HRMS: *m*/*z*: calcd for $C_{16}H_{22}N_2O$: 274.1681; found: 274.1675.

Azetidin-2-ones (3*R*)- and (3*S*)-14e: 2-Chloro-*N*-methylpyridinium iodide (219 mg, 0.83 mmol), dry TEA (0.21 mL, 1.5 mmol), and hydrazone **1e** (0.5 mmol) were added to a solution of (*S*)- or (*R*)-**12** (166 mg, 0.75 mmol) in dry toluene (7.5 mL). The reaction mixture was heated at 80 °C for 6 h and washed with water (2×8 mL), and the aqueous layer was extracted with EA (2×15 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated. Starting material, reaction times, and purification conditions are as follows.

Compound (3*R*)-14e: Preparation from acid (*R*)-**12** and, after 8 h, flash chromatography (EA/PE 2:3) gave (3*R*)-**14e** (213 mg, 94 %) as an oil (*dr* >99:1). $[\alpha]_D^{22}$ = −112.8 (*c* = 1 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, 500 MHz): δ = 0.76 (t, *J* = 7.5 Hz, 3H), 0.79 (t, *J* = 7.5 Hz, 3H), 1.31–1.45 (m, 3H), 1.53–1.65 (m, 3H), 1.71–1.78 (m, 1H), 1.83–1.90 (m, 1H), 2.76 (t, *J* = 6.7 Hz, 2H), 2.86 (dd, *J* = 2.4, 5.2 Hz, 1H), 3.15 (s, 3H), 3.42 (t, *J* = 5.2 Hz, 1H), 3.47 (dd, *J* = 6.6, 8.3 Hz, 1H), 4.13 (dd, *J* = 6.7, 8.9 Hz, 1H), 4.65 (t, *J* = 8.9 Hz, 1H), 4.72 (dd, *J* = 2.4, 5.4 Hz, 1H), 5.0 (dd, *J* = 6.7, 9 Hz, 1H), 7.27–7.39 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.8, 8.6, 24.0, 24.2, 25.9, 26.2, 48.5, 50.1, 54.5, 56.0, 59.0, 67.5, 70.8, 79.5, 127.3, 129.3, 129.4, 138.5, 157.7, 163.0 ppm; IR (KBr): $\tilde{\nu}$ = 1760, 1090, 1034 cm^{-1}; MS (EI): *m*/*z* (%): 401 (1) $[M]^+$, 300 (100), 101 (19), 91 (12); elemental analysis calcd(%) for $C_{22}H_{31}N_3O_4$: C 65.81, H 7.78, N 10.47; found C 65.83, H 7.94, N 10.41.

Compound (3*S*)-14e: Preparation from acid (*S*)-**12** and, after 8 h, flash chromatography (EA/PE 2:3) gave (3*S*)-**14e** (160 mg, 80 %) as an oil (*dr* 99:1). $[\alpha]_D^{22}$ = +38.3 (*c* = 1 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.76 (t, *J* = 7.5 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H), 1.45–1.61 (m, 7H), 1.63–1.66 (m, 1H), 1.94–1.96 (m, 1H), 2.60 (dd, *J* = 2.4, 5.2 Hz, 1H), 2.61–2.64 (m, 1H), 2.77 (t, *J* = 8.1 Hz, 1H), 3.17 (s, 3H), 3.40 (t, *J* = 5.2 Hz, 1H), 4.18 (dd, *J* = 6.7, 8.9 Hz, 1H), 4.66 (t, *J* = 9.0 Hz, 1H), 4.77 (dd, *J* = 2.4, 5.5 Hz, 1H), 5.05 (dd, *J* = 6.7, 9 Hz, 1H), 7.36–7.42 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.7, 8.6, 21.9, 23.1, 24.7, 26.0, 41.8, 50.1, 52.8, 55.6, 58.6, 65.2, 70.5, 79.4, 127.6, 129.2, 129.3, 138.3, 157.6, 163.1 ppm; IR (KBr): $\tilde{\nu}$ = 1760, 1090, 1034 cm^{-1}; MS (EI): *m*/*z* (%): 401 (1) $[M]^+$, 300 (100), 109 (18), 91 (10); elemental analysis calcd(%) for $C_{22}H_{31}N_3O_4$: C 65.81, H 7.78, N 10.47; found C 65.33, H 8.03, N 10.29.

Synthesis of 1-dialkylamino-3-(*N*-benzyl-*N*-benzyloxycarbonylamino)azetidin-2-ones 17e–g: 2-Chloro-*N*-methylpyridinium iodide (1.45 g, 5.5 mmol), dry TEA (1.4 mL, 10 mmol), and the hydrazone (2 mmol) were added dropwise to a solution of *N*-benzyl-*N*-benzyloxycarbonylglycine (**15**; 1.5 g, 5 mmol) in dry toluene (30 mL). The reaction mixture was

heated at 80 °C until the hydrazone had been consumed and was then washed with water (2×25 mL), and the aqueous layer was extracted with EA (2×25 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (Et_2O/DCM/PE) gave compounds **17**. Starting materials, reaction times, and characterization data are as follows:

(3*R*)- and (3*S*)-3-(*N*-Benzyl-*N*-benzyloxycarbonylamine)-1-[(2*S*)-2-(1-ethyl-1-methoxypropyl)pyrrolidin-1-yl]azetidin-2-one (17e): The compounds were obtained from hydrazone **1e**, the reaction mixture being heated for 23 h. Flash chromatography (Et_2O/DCM/PE 1:1:2) of the crude product (*dr* 82:18) gave (3*R*)-**17e** (720 mg, 76%) and (3*S*)-**17e** (160 mg, 16%) as oils.

Compound (3*R*)-17e: $[\alpha]_D^{21} = -32.6$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 90 °C): $\delta = 0.81$ (c, $J = 7.3$ Hz, 6H), 1.46–1.64 (m, 3H), 1.64–1.77 (m, 4H), 1.83–1.86 (m, 1H), 2.92–3.00 (m, 2H), 3.14 (s, 3H), 3.31 (dd, $J = 2.6$, 5.1 Hz, 1H), 3.37 (dd, $J = 6.7$, 8.7 Hz, 1H), 3.55 (t, $J = 5.3$ Hz, 1H), 4.47 (d, $J = 16$ Hz, 1H), 4.57 (d, $J = 16$ Hz, 1H), 4.72 (dd, $J = 2.6$, 5.3 Hz, 1H), 5.11 (d, $J = 12.8$ Hz, 1H), 5.13 (d, $J = 12.8$ Hz, 1H), 7.22–7.33 ppm (m, 10H); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 90 °C): $\delta = 7.0$, 7.3, 22.8, 23.3, 25.0, 25.2, 43.8, 48.7, 49.2, 53.1, 59.1, 66.3, 66.7, 78.7, 126.2, 126.4, 127.1, 127.5, 135.9, 137.5, 154.6, 163.2 ppm; IR (KBr): $\tilde{\nu} = 1772$, 1703, 1101, 1024 cm^{-1}; MS (CI): *m*/*z* (%): 480 (56) $[M+H]^+$, 448 (100), 378 (95), 91 (28); elemental analysis calcd (%) for $C_{28}H_{37}N_3O_4$: C 70.12, H 7.78, N 8.76; found C 70.16, H 8.07, N 8.77.

Compound (3*S*)-17e: $[\alpha]_D^{21} = -28.9$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 90 °C): $\delta = 0.80$–0.84 (m, 6H), 1.48–1.60 (m, 2H), 1.60–1.75 (m, 5H), 1.71–1.85 (m, 1H), 2.73–2.79 (m, 1H), 2.88–2.91 (m, 1H), 3.11–3.14 (m, 1H), 3.16 (s, 3H), 3.28 (dd, $J = 2.7$, 5.0 Hz, 1H), 3.51 (t, $J = 5.0$ Hz, 1H), 4.50 (d, $J = 16.0$ Hz, 1H), 4.60 (d, $J = 16.0$ Hz, 1H), 4.59 (dd, $J = 2.7$, 5.4 Hz, 1H), 5.12 (d, $J = 12.0$ Hz, 1H), 5.15 (d, $J = 12.0$ Hz, 1H), 7.24–7.33 ppm (m, 10H); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 90 °C): $\delta = 7.0$, 7.2, 22.4, 23.3, 24.7, 25.2, 43.2, 48.8, 49.6, 52.5, 59.0, 66.1, 66.4, 78.7, 126.3, 126.4, 126.9, 127.1, 127.5, 136.1, 137.5, 154.6, 163.4 ppm; IR (KBr): $\tilde{\nu} = 1772$, 1703, 1101, 1024 cm^{-1}; MS (CI): *m*/*z* (%): 480 (27) $[M+H]^+$, 448 (100), 378 (77), 91 (37); elemental analysis calcd (%) for $C_{28}H_{37}N_3O_4$: C 70.12, H 7.78, N 8.76; found C 69.61, H 7.89, N 8.73.

Compound (3*S*)-17f: This compound was prepared from **1f** with use of different proportions of reactants: hydrazone (1 mmol), acid **15** (6 mmol), 2-chloro-*N*-methylpyridinium iodide (6.6 mmol), TEA (18 mmol), and dry toluene (15 mmol). The reaction mixture was heated for 8 h at 60 °C. Flash chromatography (Et_2O/DCM/PE 1:1:2) of the crude product (*dr* >99:1) gave crystalline (3*S*)-**17f** (524 mg, 81%). M.p. 67–70 °C; $[\alpha]_D^{21} = +84.3$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 90 °C): $\delta = 3.56$ (m, 2H), 3.58 (dd, $J = 2.9$, 5.0 Hz, 1H), 3.73 (t, $J = 5.0$ Hz, 1H), 4.07 (dd, $J = 2.7$, 12.9 Hz, 2H), 4.23 (d, $J = 12.9$ Hz, 2H), 4.41 (d, $J = 2.7$ Hz, 2H), 4.56 (s, 2H), 4.74 (dd, $J = 2.9$, 5.5 Hz, 1H), 5.16 (s, 2H), 5.55 (s, 2H), 7.22–7.43 ppm (m, 20H); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 90 °C): $\delta = 47.1$, 52.1, 57.8 (2C), 60.7, 65.7 (2C), 67.8, 78.4 (2C), 99.4 (2C), 126.3–129.3 (m), 137.4, 138.9, 139.2, 155.9, 168.7 ppm; IR (KBr): $\tilde{\nu} = 1773$, 1701, 1393, 1099 cm^{-1}; MS (EI): *m*/*z* (%): 647 (0.5) $[M]^+$, 556 (70), 105 (38), 91 (100); elemental analysis calcd (%) for $C_{38}H_{37}N_3O_7$: C 70.46, H 5.76, N 6.49; found C 70.76, H 6.15, N 6.21.

Compound (3*R*)-17g: This compound was prepared from **1g**, but with use of the following proportions of reagents: hydrazone (1 mmol), acid **15** (2.5 mmol), 2-chloro-*N*-methylpyridinium iodide (2.8 mmol), TEA (5 mmol), and dry toluene (13 mL). Flash chromatography (Et_2O/PE 1:1) of the crude product (*dr* >99:1) gave (3*S*)-**17f** (326 mg, 80%) as an oil. $[\alpha]_D^{24} = -38.0$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, [D$_6$]DMSO, 90 °C): $\delta = 0.99$ (d, $J = 6.3$ Hz, 6H), 1.24–1.34 (m, 2H), 1.87–1.95 (m, 2H), 3.38–3.45 (m, 3H), 3.49 (dd, $J = 2.8$, 5.1 Hz, 1H)), 4.48 (d, $J = 16.1$ Hz, 1H), 4.58 (d, $J = 16.1$ Hz, 1H), 4.84 (dd, $J = 2.8$, 5.4 Hz, 1H), 5.12 (d, $J = 13.1$ Hz, 1H), 5.16 (d, $J = 13.1$ Hz, 1H), 7.23–7.31 ppm (m, 10H); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 90 °C): $\delta = 17.8$ (2C), 29.4 (2C), 49.9 (3C), 55.4, 59.3, 66.4, 126.4, 126.5, 126.9, 127.2, 127.7, 136.0, 137.5, 154.6, 164.9 ppm; IR (KBr): $\tilde{\nu} = 1776$, 1712, 1458, 1100, 1024 cm^{-1}; MS (CI): *m*/*z* (%): 408 (100) $[M+H]^+$, 316 (44), 91 (42); HRMS: *m*/*z*: calcd for $C_{24}H_{30}N_3O_3$: 408.2287; found: 408.2287.

Synthesis of *cis*-4-alkyl(aryl)-1-(*N*,*N*-dialkylamino)-3-benzyloxy-azetidin-2-ones 23e–27e: A solution of benzyloxyacetyl chloride (**2**; 0.4 M, 1 mL, 6 mmol) in dry toluene (15 mL) was added in small portions over 3 h to a solution of the appropriate hydrazone (**18e**–**22e**, 1.5 mmol) and TEA (1.7 mL, 12 mmol) in dry toluene (8 mL). The reaction mixture was heated until the hydrazone had been consumed and washed with water (2×25 mL), and the aqueous layer was extracted with EA (2×25 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (Et_2O/DCM/PE) gave the β-lactams **23**–**27e**. Starting materials, reaction times, and characterization data are as follows:

(3*R*,4*S*)- and (3*R*,4*R*)-3-Benzyloxy-1-[(2*S*)-2-(1-ethyl-1-methoxypropyl)-pyrrolidin-1-yl]-4-pentylazetidin-2-one (23e): These compounds were prepared from hydrazone **18e**, the reaction mixture being heated at 80 °C for 8 h. Flash chromatography (Et_2O/DCM/PE 1:1:6) of the crude product (*dr* 82:18 and *cis*/*trans* 98:2) gave (3*R*,4*S*)-**23e** (435 mg, 70%) and (3*S*,4*R*)-**23e** (95 mg, 15%).

Compound (3*R*,4*S*)-23e: $[\alpha]_D^{24} = +6.6$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.84$–0.91 (m, 9H), 1.29–1.37 (m, 4H), 1.41–1.53 (m, 4H), 1.53–1.59 (m, 2H), 1.68–1.75 (m, 2H), 1.68–1.78 (m, 2H), 1.96–2.03 (m, 2H), 3.17–3.21 (m, 1H), 3.21 (s, 3H), 3.25–3.31 (m, 1H), 3.73–3.78 (m, 2H), 4.38 (d, $J = 4.8$ Hz, 1H), 4.67 (d, $J = 11.9$ Hz, 1H), 4.85 (d, $J = 11.9$ Hz, 1H), 7.28–7.36 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 7.9$, 8.5, 13.9, 22.5, 24.3 (2C), 25.8, 26.2, 26.4, 28.5, 31.9, 49.8, 56.7, 61.9, 67.7, 72.6, 79.1, 79.6, 127.6, 127.7, 128.3, 137.6, 166.4 ppm; IR (KBr): $\tilde{\nu} = 1751$, 1468, 1103 cm^{-1}; MS (EI): *m*/*z* (%): 416 (2) $[M]^+$, 315 (41), 111 (100), 91 (30); elemental analysis calcd (%) for $C_{25}H_{40}N_2O_3$: C 72.08, H 9.68, N 6.72; found C 72.12, H 9.25, N 6.92.

Compound (3*S*,4*R*)-23e: $[\alpha]_D^{24} = -96.3$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.83$–0.91 (m, 9H), 1.25–1.50 (m, 4H), 1.52–1.67 (m, 4H), 1.71–1.96 (m, 8H), 2.92–3.0 (m, 1H), 3.26 (s, 3H), 3.27–3.32 (m, 1H), 3.39–3.44 (m, 1H), 3.93 (dt, $J = 5.1$, 8.6 Hz, 1H), 4.34 (d, $J = 5.1$ Hz, 1H), 4.70 (d, $J = 11.9$ Hz, 1H), 4.92 (d, $J = 11.9$ Hz, 1H), 7.27–7.37 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 7.8$, 8.5, 13.9, 22.4, 23.3, 23.5, 25.6, 25.9, 26.2, 28.8, 31.8, 50.2, 55.7, 59.4, 65.3, 72.4, 78.4, 79.7, 127.6, 127.8, 128.0, 137.6, 166.9 ppm; IR (KBr): $\tilde{\nu} = 1751$, 1468, 1103 cm^{-1}; MS (CI): *m*/*z* (%): 417 (37) $[M+H]^+$, 385 (100), 181 (98), 91 (76); elemental analysis calcd (%) for $C_{25}H_{40}N_2O_3$: C 72.08, H 9.68, N 6.72; found C 71.81, H 9.73, N 6.50.

(3*R*,4*S*)- and (3*S*,4*R*)-3-Benzyloxy-4-isobutyl-1-[(2*S*)-2-(1-ethyl-1-methoxypropyl)pyrrolidin-1-yl]azetidin-2-one (24e): These compounds were prepared from **19e**, the reaction mixture being heated at 80 °C for 8 h. Flash chromatography (Et_2O/DCM/PE 1:1:6) of the crude product (*dr* 87:13 and *cis*/*trans* 98:2) gave (3*R*,4*S*)-**24e** (441 mg, 73%) and (3*S*,4*R*)-**24e** (66 mg, 11%).

Compound (3*R*,4*S*)-24e: $[\alpha]_D^{26} = +10.8$ ($c = 1.5$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 7.5$ Hz, 3H), 0.88 (t, $J = 7.5$ Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 3H), 0.96 (d, $J = 6.6$ Hz, 3H), 1.43–1.63 (m, 6H), 1.66–1.76 (m, 2H), 1.82 (q, $J = 6.6$ Hz, 1H), 1.95–2.02 (m, 2H), 3.14–3.22 (m, 1H), 3.21 (s, 3H), 3.25–3.31 (m, 1H), 3.73–3.78 (m, 1H), 3.86 (dt, $J = 4.8$, 6.6 Hz, 1H), 4.40 (d, $J = 4.8$ Hz, 1H), 4.67 (d, $J = 11.9$ Hz, 1H), 4.86 (d, $J = 11.9$ Hz, 1H), 7.27–7.36 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 7.8$, 8.3, 22.5, 23.0 (2C), 24.2, 25.1, 26.1 (2C), 36.9, 49.6, 56.6, 60.1, 67.6, 72.4, 78.9, 79.5, 127.5, 127.6, 128.2, 137.4, 166.2 ppm; IR (KBr): $\tilde{\nu} = 1751$, 1467, 1094 cm^{-1}; MS (CI): *m*/*z* (%): 403 (72) $[M+H]^+$, 371 (64), 301 (100), 91 (24); elemental analysis calcd (%) for $C_{24}H_{38}N_2O_3$: C 71.60, H 9.51, N 6.96; found C 71.53, H 9.87, N 7.13.

Compound (3*S*,4*R*)-24e: $[\alpha]_D^{26} = -106.8$ ($c = 1.2$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 7.5$ Hz, 3H), 0.88 (t, $J = 7.5$ Hz, 3H), 0.94 (d, $J = 6.3$ Hz, 3H), 0.95 (d, $J = 6.3$ Hz, 3H), 1.49–1.69 (m, 4H), 1.70–1.83 (m, 6H), 1.85–1.97 (m, 1H), 2.92–3.0 (m, 1H), 3.22–3.32 (m, 1H), 3.26 (s, 3H), 3.42–3.47 (m, 1H), 4.0–4.30 (m, 1H), 4.35 (d, $J = 5.1$ Hz, 1H), 4.70 (d, $J = 11.9$ Hz, 1H), 4.90 (d, $J = 11.9$ Hz, 1H), 7.26–7.38 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 7.6$, 8.5, 22.4, 23.0, 23.3, 23.5 (2C), 25.7, 26.1, 37.0, 50.1, 55.8, 57.9, 65.2, 72.3, 78.5, 79.7, 127.5, 127.9, 128.2, 137.5, 166.8 ppm; IR (KBr): $\tilde{\nu} = 1751$, 1467, 1094 cm^{-1}; MS (CI): *m*/*z* (%): 403 (93) $[M+H]^+$, 371 (100), 301 (84), 91 (55); elemental analysis calcd (%) for $C_{24}H_{38}N_2O_3$: C 71.60, H 9.51, N 6.96; found C 71.81, H 9.57, N 6.74.

(3*R*,4*S*)- and (3*S*,4*R*)-3-Benzyloxy-1-[(2*S*)-2-(1-ethyl-1-methoxypropyl)-pyrrolidin-1-yl]-4-phenylethylazetidin-2-one (25e): These compounds were prepared from **20e**, the reaction mixture being heated at 80 °C for 9 h. Flash chromatography (EA/PE 1:6) of the crude product (*dr* 80:20 and *cis*/*trans* >99:1) gave (3*R*,4*S*)-**25e** (524 mg, 78 %) and (3*S*,4*R*)-**25e** (131 mg, 19 %).

Compound (3*R*,4*S*)-25e: $[\alpha]_D^{28} = +19$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.83$ (q, $J = 7.7$ Hz, 6H), 1.41–1.55 (m, 4H), 1.66–1.73 (m, 2H), 1.95–2.06 (m, 4H), 2.72–2.77 (m, 2H), 3.17 (s, 3H), 3.18–3.23 (m, 1H), 3.28–3.37 (m, 1H), 3.72–3.75 (m, 1H), 3.78–3.82 (m, 1H), 4.41 (d, $J = 4.8$ Hz, 1H), 4.67 (d, $J = 11.9$ Hz, 1H), 4.89 (d, $J = 11.9$ Hz, 1H), 7.15–7.37 ppm (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 7.9$, 8.6, 24.3, 24.4, 26.3 (2C), 30.5, 32.3, 49.8, 56.8, 61.2, 67.9, 72.7, 78.9, 79.7, 126, 127.7–128.4 (m), 137.5, 141.8, 166.4 ppm; IR (KBr): $\tilde{\nu} = 1751$, 1406, 1101 cm^{-1}; MS (CI): *m*/*z* (%): 451 (98) $[M+H]^+$, 419 (100), 349 (77), 91 (30); elemental analysis calcd (%) for $C_{28}H_{38}N_2O_3$: C 74.63, H 8.50, N 6.22; found C 74.50, H 8.75, N 6.26.

Compound (3*S*,4*R*)-25e: $[\alpha]_D^{28} = -57.4$ ($c = 1.2$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.86$ (q, $J = 7.4$ Hz, 6H), 1.51–1.64 (m, 4H), 1.73–1.82 (m, 3H), 1.89–1.94 (m, 1H), 2.11–2.22 (m, 2H), 2.60–2.66 (m, 1H), 2.72–2.84 (m, 1H), 2.93–2.98 (m, 1H), 3.24 (s, 3H), 3.26–3.30 (m, 1H), 3.40–3.42 (m, 1H), 3.98–4.01 (m, 1H), 4.40 (d, $J = 5.1$ Hz, 1H), 4.74 (d, $J = 11.9$ Hz, 1H), 4.98 (d, $J = 11.9$ Hz, 1H), 7.16–7.41 ppm (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 7.8$, 8.6, 23.5 (2C), 25.7, 26.2, 30.7, 32.3, 50.1, 55.8, 58.5, 65.4, 72.6, 78.4, 79.8, 125.9, 127.7–128.6 (m), 137.5, 141.5, 166.9 ppm; IR (KBr): $\tilde{\nu} = 1751$, 1406, 1101 cm^{-1}; MS (CI): *m*/*z* (%): 451 (47) $[M+H]^+$, 419 (80), 349 (41), 138 (100), 91 (98); HRMS: *m*/*z*: calcd for $C_{28}H_{39}N_2O_3$: 451.2961; found: 451.2954.

(3*R*,4*S*)- and (3*S*,4*R*)-3-Benzyloxy-1-[(2*S*)-2-(1-ethyl-1-methoxypropyl)-pyrrolidin-1-yl]-4-isopropylazetidin-2-one (26e): These compounds were prepared from **21e**, the reaction mixture being heated at 100 °C for 7.5 h. Flash chromatography (Et_2O/PE 1:3) of the crude product (*dr* 91:9 and *cis*/*trans* >99:1) gave (3*R*,4*S*)-**26e** (477 mg, 82 %) and (3*S*,4*R*)-**26e** (47 mg, 8 %).

Compound (3*R*,4*S*)-26e: $[\alpha]_D^{23} = +13.9$ ($c = 1.1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.82$–0.94 (m, 6H), 0.99 (d, $J = 6.6$ Hz, 3H), 1.13 (d, $J = 6.6$ Hz, 3H), 1.47–1.59 (m, 4H), 1.63–1.74 (m, 2H), 1.96–2.09 (m, 3H), 3.18 (s, 3H), 3.21–3.31 (m, 1H), 3.32–3.38 (m, 1H), 3.51 (dd, $J = 5.0$, 8.8 Hz, 1H), 3.76–3.81 (m, 1H), 4.38 (d, $J = 5.0$ Hz, 1H), 4.69 (d, $J = 11.9$ Hz, 1H), 4.93 (d, $J = 11.9$ Hz, 1H), 7.27–7.32 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 7.6$, 8.5, 19.5 (2C), 24.0, 24.1, 26.3, 26.4, 28.4, 49.5, 56.8, 67.3, 67.8, 72.4, 78.9, 79.6, 127.4, 127.5, 128.2, 137.6, 166.9 ppm; IR (KBr): $\tilde{\nu} = 1746$, 1461, 1088, 1034 cm^{-1}; MS (CI): *m*/*z* (%): 389 (82) $[M+H]^+$, 357 (83), 287 (100), 91 (15); elemental analysis calcd (%) for $C_{23}H_{36}N_2O_3$: C 71.10, H 9.34, N 7.21; found C 71.05, H 9.40, N 7.28.

Compound (3*S*,4*R*)-26e: $[\alpha]_D^{28} = -72.7$ ($c = 0.9$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 7.6$ Hz, 3H), 0.90 (t, $J = 7.6$ Hz, 3H), 1.08 (d, $J = 7.0$ Hz, 3H), 1.12 (d, $J = 7.0$ Hz, 3H), 1.52–1.68 (m, 4H), 1.73–1.83 (m, 3H), 1.85–1.95 (m, 1H), 2.07–2.18 (m, 1H), 2.89–2.97 (m, 1H), 3.22 (s, 3H), 3.29–3.35 (m, 1H), 3.47 (dd, $J = 5.7$, 9.1 Hz, 1H), 3.85 (t, $J = 5.4$ Hz, 1H), 4.33 (d, $J = 5.4$ Hz, 1H), 4.68 (d, $J = 11.9$ Hz, 1H), 4.94 (d, $J = 11.9$ Hz, 1H), 7.27–7.38 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 7.7$, 8.7, 18.7, 19.6 (2C), 22.8, 23.4, 28.2, 50.0, 55.2, 64.2, 64.5, 78.9, 80.0 (2C), 127.4, 127.5, 128.2, 137.6, 168.2 ppm; IR (KBr): $\tilde{\nu} = 1746$, 1461, 1088, 1034 cm^{-1}; MS (CI): *m*/*z* (%): 389 (60) $[M+H]^+$, 357 (75), 287 (100), 181 (71); HRMS: *m*/*z*: calcd for $C_{23}H_{36}N_2O_3$: 388.2726; found: 388.2718.

(3*R*,4*S*)- and (3*S*,4*R*)-3-Benzyloxy-1-[(2*S*)-2-(1-ethyl-1-methoxypropyl)-pyrrolidin-1-yl]-4-phenylazetidin-2-one (27e): These compounds were prepared from **22e**, the reaction mixture being heated at 100 °C for 8 h. Flash chromatography (EA/PE 1:4) of the crude product (*dr* 76:24 and *cis*/*trans* >99:1) gave crystalline (3*R*,4*S*)-**27e** (472 mg, 75 %) and crystalline (3*S*,4*R*)-**27e** (149 mg, 23 %).

Compound (3*R*,4*S*)-27e: m.p. 72–74 °C; $[\alpha]_D^{25} = +76.7$ ($c = 1.1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.78$ (t, $J = 7.5$ Hz, 3H), 0.86 (t, $J = 7.5$ Hz, 3H), 1.40–1.55 (m, 2H), 1.58–1.70 (m, 4H), 1.80–2.0 (m, 2H), 3.10–3.36 (m, 1H), 3.21 (s, 3H), 3.35–3.43 (m, 1H), 3.73–3.78 (m, 1H), 4.09 (d, $J = 11.1$ Hz, 1H), 4.24 (d, $J = 11.1$ Hz, 1H), 4.62 (d, $J = 4.5$ Hz, 1H), 4.90 (d, $J = 4.5$ Hz, 1H), 6.93–7.23 (m, 5H), 7.36–7.49 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 7.6$, 8.7, 23.6, 24.3, 25.8, 26.0, 49.6, 55.6, 65.6, 66.5, 72.1, 79.8, 80.1, 127.7–129.2 (m), 134.6, 136.3, 165.7 ppm; IR (KBr): $\tilde{\nu} = 1768$, 1458, 1092 cm^{-1}; MS (CI): *m*/*z* (%): 423 (59) $[M+H]^+$, 321 (41), 213 (53), 181 (100); elemental analysis calcd (%) for $C_{26}H_{34}N_2O_3$: C 73.90, H 8.11, N 6.63; found C 73.83, H 8.17, N 6.74.

Compound (3*S*,4*R*)-27e: m.p. 74–76 °C; $[\alpha]_D^{25} = -159.8$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 7.5$ Hz, 3H), 0.93 (t, $J = 7.5$ Hz, 3H), 1.24–1.33 (m, 1H), 1.45–1.61 (m, 2H), 1.63–1.77 (m, 5H), 2.46–2.55 (m, 1H), 3.0–3.07 (m, 1H), 3.17–3.20 (m, 1H), 3.22 (s, 3H), 4.09 (d, $J = 11.2$ Hz, 1H), 4.25 (d, $J = 11.2$ Hz, 1H), 4.53 (d, $J = 4.8$ Hz, 1H), 5.08 (d, $J = 4.8$ Hz, 1H), 6.92–6.98 (m, 5H), 7.18–7.54 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 7.5$, 9.1, 21.8, 23.3, 24.9, 26.0, 49.9, 54.9, 60.5, 64.9, 72.2, 80.1 (2C), 127.7–129.1 (m), 135.4, 136.3, 166.7 ppm; IR (KBr): $\tilde{\nu} = 1768$, 1458, 1092 cm^{-1}; MS (CI): *m*/*z* (%): 423 (37) $[M+H]^+$, 321 (36), 213 (61), 181 (100); elemental analysis calcd (%) for $C_{26}H_{34}N_2O_3$: C 73.90, H 8.11, N 6.63; found C 73.90, H 8.29, N 6.46.

2-Benzyloxy-*N*-[(2*S*)-2-(1-ethyl-1-methoxypropyl)pyrrolin-1-yl]acetamide (28): A solution of benzyloxyacetyl chloride (**2**, 0.4 mmol, 0.07 mL) in dry toluene (1 mL, 0.4 M) was added dropwise at rt to a solution of the hydrazone **18e** (0.2 mmol) and TEA (0.8 mmol, 0.12 mL) in dry toluene (2 mL). The mixture was stirred at rt until TLC showed no change. The reaction mixture was washed with water (2×25 mL), and the aqueous layer was extracted with EA (2×25 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (Et_2O/DCM/PE 1:1:1) gave **28** (50 mg, 75 %) as an oil. $[\alpha]_D^{21} = -25.3$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 7.5$ Hz, 3H), 0.88 (t, $J = 7.5$ Hz, 3H), 1.49–1.66 (m, 4H), 1.77–1.98 (m, 4H), 2.27–2.65 (m, 1H), 3.09–3.13 (m, 1H), 3.23 (s, 3H), 3.41–3.49 (m, 1H), 3.98 (s, 2H), 4.56 (s, 2H), 7.32–7.38 (m, 5H), 7.9 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 7.9$, 8.4, 22.2, 24.2, 24.9, 26.2, 49.2, 56.3, 69.2, 69.5, 73.5, 79.8, 127.8, 128.1, 128.5, 136.8, 166.4 ppm; IR (KBr): $\tilde{\nu} = 1683$, 1412, 1022 cm^{-1}; MS (CI): *m*/*z* (%): 335 (17) $[M+H]^+$, 305 (75), 303 (71), 287 (100); elemental analysis calcd (%) for $C_{19}H_{30}N_2O_3$: C 68.23, H 9.04, N 8.38; found C 68.27, H 9.39, N 8.43. From **20e**, the same product was obtained in 68 % yield, and with identical characterization data.

Synthesis of 27f, 30f, and 19h—General procedure: A solution of benzyloxyacetyl chloride (**2**, 0.4 mL, 2.4 mmol) in dry toluene (4.8 mL) was added in 12 portions (each 0.4 mL, 0.2 mmol) at 30 min intervals to a solution of hydrazones **22f**, **19f**, or **19h** (0.4 mmol) and TEA (0.67 mL, 4.8 mmol) in dry toluene (1.7 mL). The reaction mixture was heated at 100 °C until the hydrazone had been consumed (8.5 h) and washed with water (2×25 mL), and the aqueous layer was extracted with EA (2×25 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated.

Compound 27f: This compound was prepared from **22f**, flash chromatography (EA/PE 1:2) providing crystalline (3*S*,4*R*)-**27f** (151 mg, 66 %, *dr* >99:1). M.p. 78–80 °C; $[\alpha]_D^{23} = +4.4$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 90 °C): $\delta = 3.43$ (br s, 2H), 3.95–3.98 (m, 2H), 4.04 (d, $J = 11.4$ Hz, 1H), 4.23–4.32 (m, 5H), 5.0 (d, $J = 4.9$ Hz, 1H), 5.35 (d, $J = 4.9$ Hz, 1H), 5.54 (s, 2H), 6.96–6.98 (m, 5H), 7.20–7.29 (m, 5H), 7.31–7.45 ppm (m, 10H); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 90 °C): $\delta = 57.7$ (2C), 65.4, 67.1, 72.6, 78.1 (2C), 80.9, 99.2, 126.9, 130.4, 137.8, 139.1, 168.9 ppm; IR (KBr): $\tilde{\nu} = 1776$, 1394, 1092, 1021 cm^{-1}; MS (CI): *m*/*z* (%): 591 (18), $[M+H]^+$, 381 (92), 107 (71), 91 (100); HRMS: *m*/*z*: calcd for $C_{36}H_{35}N_2O_6$: 591.2495; found: 591.2487; elemental analysis calcd (%) for $C_{36}H_{34}N_2O_6$: C 73.20, H 5.80, N 4.74; found C 73.23, H 6.24, N 4.46.

Compound 30: This compound was prepared from **19f**, flash chromatography (Et_2O/DCM/PE 1:1:4) providing **30** (196 mg, 86 %) as an oil. $[\alpha]_D^{25} = +50.6$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (d, $J = 6.7$ Hz, 3H), 0.94 (d, $J = 6.7$ Hz, 3H), 2.20–2.33 (m, 1H), 3.55–3.57 (m, 1H), 3.89–3.91 (m, 1H), 3.97–4.03 (m, 3H), 4.20–4.26 (m, 1H), 4.23 (d, $J = 16.1$ Hz, 1H), 4.46–4.50 (m, 2H), 4.51 (d, $J = 11.7$ Hz, 1H), 4.67 (d, $J = 11.7$ Hz, 1H), 5.02 (d, $J = 16.1$ Hz, 1H), 5.49 (s, 1H), 5.53 (s, 1H), 5.99 (dd, $J = 7.1$, 14.7 Hz, 1H), 6.73 (dd, $J = 0.9$, 14.7 Hz, 1H), 7.25–7.49 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.6$, 22.7, 29.5, 52.6, 54.9, 63.9, 64.2, 68.3, 72.9, 77.2 (2C), 98.9, 99.6, 120.3, 125.4, 129.1, 137.4, 137.5, 137.7, 173.3 ppm; IR (KBr): $\tilde{\nu} = 1691$, 1387, 1128, 1012 cm^{-1}; MS (EI): *m*/*z* (%): 570 (28), $[M]^+$, 421 (100), 338 (37), 91

(64); elemental analysis calcd (%) for $C_{34}H_{38}N_2O_6$: C 71.56, H 6.71, N 4.91; found C 71.96, H 7.29, N 4.58.

Compound 24h: This compound was prepared from **19h**, but with heating at 80 °C for 22 h. Flash chromatography (EA/PE 1:10) of the crude product (*de* 98 %, *cis*/*trans* 9:1) gave (3*R*,4*S*)-**24h** (96 mg, 53 %, *cis*/*trans* >99:1) as an oil; $[\alpha]_D^{24} = -80.7$ ($c = 1.5$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.80$ (t, $J = 6.8$ Hz, 6H), 1.03–1.23 (m, 2H), 1.55–1.65 (m, 1H), 2.04–2.15 (m, 2H), 2.38–2.48 (m, 2H), 2.95 (dt, $J = 5.1$, 6.8 Hz, 1H), 3.96 (d, $J = 5.1$ Hz, 1H), 4.37 (d, $J = 11.9$ Hz, 1H), 4.51 (d, $J = 11.9$ Hz, 1H), 4.87–4.92 (m, 2H), 7.13–7.60 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.3$, 22.7, 25.1, 32.5 (2C), 36.7, 61.9, 65.8 (2C), 71.6, 78.1, 127.3, 128.5, 137.6, 141.3, 166.9 ppm; IR (KBr): $\tilde{\nu} = 1752$, 1458, 1371, 1103 cm^{-1}; MS (CI): *m*/*z* (%): 455 (84), $[M+H]^+$, 265 (100), 104 (32), 91 (55); HRMS: *m*/*z*: calcd for $C_{30}H_{35}N_2O_2$: 455.2699; found: 455.2691.

General procedure for compounds (3*R*,4*S*)-24–27g: Small amounts (0.63 mL, 0.25 mmol) of a solution of benzyloxyacetyl chloride (**2**, 0.33 mL, 2 mmol) in dry toluene (0.4 M, 5 mL) were added every 30 min over 4 h to a solution of hydrazone **19**–**22g** (0.5 mmol) and TEA (0.6 mL, 4 mmol) in dry toluene (2.5 mL). The reaction mixture was heated until the starting hydrazone had been consumed and then washed with water (2×25 mL), and the aqueous layer was extracted with EA (2×25 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (Et_2O/DCM/PE 1:1:8) gave β-lactams **24**–**27g**: Starting materials, reaction times, and characterization data are as follows:

(3*R*,4*S*)-*cis*-3-Benzyloxy-4-isobutyl-1-[(2*R*,5*R*)-2,5-dimethyl-pyrrolidin-1-yl]azetidin-2-one (24g): This compound was prepared from **19g**, the reaction mixture being heated for 8.5 h at 60 °C. Flash chromatography (Et_2O/DCM/PE 1:1:8) gave (3*R*,4*S*)-**24g** (*cis*/*trans* 95:5, 116 mg, 70 %) as an oil. $[\alpha]_D^{23} = +28.1$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (d, $J = 6.5$ Hz, 3H), 0.95 (d, $J = 6.5$ Hz, 3H), 1.08 (d, $J = 6.3$ Hz, 6H), 1.36–1.42 (m, 2H), 1.59–1.65 (m, 2H), 1.70–1.80 (m, 1H), 1.90–2.0 (m, 2H), 3.67–3.76 (m, 3H), 4.53 (d, $J = 5.0$ Hz, 1H), 4.71 (d, $J = 11.9$ Hz, 1H), 4.89 (d, $J = 11.9$ Hz, 1H), 7.27–7.38 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.8$ (2C), 22.7, 22.8, 25.5, 30.3 (2C), 37.0, 56.3 (2C), 63.1, 72.3, 78.2, 127.5, 127.6, 128.2, 137.4, 167.8 ppm; IR (KBr): $\tilde{\nu} = 1751$, 1362, 1108 cm^{-1}; MS (CI): *m*/*z* (%): 331 (27) $[M+H]^+$, 330 (10), 141 (100), 91 (63); elemental analysis calcd (%) for $C_{20}H_{30}N_2O_2$: C 72.69, H 9.15, N 8.48; found C 72.81, H 9.52, N 8.47.

(3*R*,4*S*)-*cis*-3-Benzyloxy-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-4-phenylethylazetidin-2-one [(3*R*,4*S*)-25g]: This compound was prepared from **20g**, the reaction mixture being heated for 6 h at 60 °C. Flash chromatography (Et_2O/DCM/PE 1:1:6) gave (3*R*,4*S*)-**25g** (157 mg, 83 %) as an oil. $[\alpha]_D^{23} = +23.5$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.10$ (d, $J = 6.3$ Hz, 6H), 1.93–2.12 (m, 4H), 2.63–2.80 (m, 4H), 3.60–3.80 (m, 3H), 4.58 (d, $J = 5.0$ Hz, 1H), 4.73 (d, $J = 11.9$ Hz, 1H), 4.93 (d, $J = 11.9$ Hz, 1H), 7.18–7.42 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.7$ (2C), 29.9 (2C), 30.9, 32.0, 56.4 (2C), 63.7, 72.4, 78.1, 125.8, 127.6, 127.7, 128.3, 128.4, 137.4, 141.5, 167.7 ppm; IR (KBr): $\tilde{\nu} = 1746$, 1456, 1355, 1112 cm^{-1}; MS (CI): *m*/*z* (%): 379 (100) $[M+H]^+$, 378 (42), 141 (37), 91 (23); elemental analysis calcd (%) for $C_{24}H_{30}N_2O_2$: C 76.16, H 7.99, N 7.40; found C 76.04, H 8.26, N 7.37.

(3*R*,4*S*)-*cis*-3-Benzyloxy-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-4-isopropylazetidin-2-one [(3*R*,4*S*)-26g]: This compound was prepared from **21g**, the reaction mixture being heated for 6.5 h at 80 °C. Flash chromatography (Et_2O/DCM/PE 1:1:12) gave (3*R*,4*S*)-**26g** (127 mg, 80 %) as an oil. $[\alpha]_D^{23} = +59.6$ ($c = 1.1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.98$ (d, $J = 6.3$ Hz, 3H), 1.07 (d, $J = 6.3$ Hz, 3H), 1.09 (d, $J = 6.7$ Hz, 6H), 1.31–1.38 (m, 2H), 1.89–2.09 (m, 3H), 3.32 (dd, $J = 5.3$, 8.6 Hz, 1H), 3.69–3.80 (m, 2H), 4.54 (d, $J = 5.3$ Hz, 1H), 4.72 (d, $J = 12.0$ Hz, 1H), 4.93 (d, $J = 12.0$ Hz, 1H), 7.27–7.38 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.0$ (2C), 19.2 (2C), 28.3, 30.1 (2C), 56.0 (2C), 70.7, 72.3, 78.2, 127.4, 127.5, 128.2, 137.6, 169.9 ppm; IR (KBr): $\tilde{\nu} = 1752$, 1355, 1108 cm^{-1}; MS (EI): *m*/*z* (%): 316 (6) $[M]^+$, 225 (13), 140 (29), 91 (100); elemental analysis calcd (%) for $C_{19}H_{28}N_2O_2$: C 72.12, H 8.92, N 8.85; found C 72.51, H 9.23, N 8.87.

(3*R*,4*S*)-*cis*-3-Benzyloxy-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-4-phenyl-azetidin-2-one [(3*R*,4*S*)-27g]: This compound was prepared from **22g**, the reaction mixture being heated for 5.5 h at 100 °C. Flash chromatography (Et_2O/DCM/PE 1:1:6) gave crystalline (3*R*,4*S*)-**27g** (168 mg, 96 %). M.p. 90–92 °C; $[\alpha]_D^{23} = +116.8$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.15$ (d, $J = 6.3$ Hz, 6H), 1.26–1.36 (m, 2H), 1.83–1.95 (m, 2H), 3.60–3.70 (m, 2H), 4.14 (d, $J = 11.2$ Hz, 1H), 4.25 (d, $J = 11.2$ Hz, 1H), 4.71 (d, $J = 4.7$ Hz, 1H), 4.78 (d, $J = 4.7$ Hz, 1H), 6.95–6.98 (m, 5H), 7.21–7.24 (m, 5H), 7.34–7.49 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.7$ (2C), 28.8 (2C), 55.5 (2C), 68.7, 72.1, 79.9, 127.7, 128.1, 128.2, 128.3, 128.4, 134.5, 136.3, 167.0 ppm; IR (KBr): $\tilde{\nu} = 1752$, 1593, 1442, 1371, 1108 cm^{-1}; MS (CI): *m*/*z* (%): 351 (28) $[M+H]^+$, 231 (10), 141 (100), 91 (21); elemental analysis calcd (%) for $C_{22}H_{26}N_2O_2$: C 75.40, H 7.48, N 7.99; found C 75.40, H 7.59, N 7.86.

Oxidative deamination—General procedure: MMPP·6H_2O (524 mg, 0.9 mmol) was added to a solution of *N*-protected β-lactam (0.3 mmol) in MeOH (0.4 M, 0.75 mL). The reaction mixture was vigorously stirred until the starting material had been consumed. The mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (4×10 mL). The organic layer was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography. Eluents, yields, and spectral and analytical data for compounds (3*R*)-**33**, (3*S*)-**33**, (3*R*)-**34**, (3*S*)-**34**, (3*R*)-**35**, (3*S*)-**35**, (3*R*,4*S*)-**36**, (3*R*,4*S*)-**37**, (3*R*,4*S*)-**38**, (3*R*,4*S*)-**39** and (3*R*,4*S*)-**40** are as follows.

(3*R*)-3-Benzyloxyazetidin-2-one [(3*R*)-33]: This compound was prepared from (3*R*)-**4e**, flash chromatography (toluene/EA 3:2) providing crystalline (3*R*)-**33** (47 mg, 89 %): M.p. 80–82 °C; $[\alpha]_D^{22} = +54.9$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.28$ (dd, $J = 2.2$, 4.9 Hz, 1H), 3.47 (t, $J = 4.9$ Hz, 1H), 4.67 (d, $J = 11.6$ Hz, 1H), 4.81–4.84 (m, 1H), 4.86 (d, $J = 11.6$ Hz, 1H), 5.93 (br s, 1H), 7.3–7.4 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 44.1$, 72.2, 82.5, 128.1, 128.5, 136.9, 168.3 ppm; IR (KBr): $\tilde{\nu} = 3311$, 1731, 1461 cm^{-1}; MS (CI): *m*/*z* (%): 178 (100) $[M+H]^+$, 150 (31), 91 (84); elemental analysis calcd (%) for $C_{10}H_{11}NO_2$: C 67.78, H 6.23, N 7.90; found C 67.45, H 6.25, N 7.90.

The same product was obtained, in 82 % yield, from (3*R*)-**4g**, and MMPP·6H_2O (99 mg, 0.17 mmol), and had identical characterization data.

(3*S*)-3-Benzyloxyazetidin-2-one [(3*S*)-33]: This compound was prepared from (3*S*)-**4f**, flash chromatography (toluene/EA 3:2) providing crystalline (3*S*)-**33** (44 mg, 82 %). $[\alpha]_D^{22} = -55.9$ ($c = 0.9$ in CH_2Cl_2); MS (CI): *m*/*z* (%): 178 (56) $[M+H]^+$, 150 (19), 91 (100); HRMS: *m*/*z*: calcd for $C_{10}H_{11}NO_2$: 178.068; found: 178.0866. The rest of spectral and analytical data were in agreement with those described for (3*R*)-**33**.

(3*S*)-3-[(*S*)-(5-Phenyloxazolidin-1-yl-2-one)]azetidin-2-one [(3*S*)-34]: This compound was prepared from (3*S*)-**14e**, flash chromatography (DCM/MeOH 20:1) providing crystalline (3*S*)-**34** (50 mg, 71 %). M.p. 156–158 °C; $[\alpha]_D^{22} = +76.3$ ($c = 1.1$ in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.76$ (dd, $J = 2.8$, 5.6 Hz, 1H), 3.32 (t, $J = 5.6$ Hz, 1H), 4.24 (dd, $J = 6.7$, 9.0 Hz, 1H), 4.70 (t, $J = 9.0$ Hz, 1H), 5.01 (dd, $J = 6.7$, 9.0 Hz, 1H), 5.06 (ddd, $J = 0.5$, 2.8, 5.5 Hz, 1H), 5.63 (br s, 1H), 7.39–7.43 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 42.0$, 59.0, 60.9, 70.4, 127.4, 129.3, 129.5, 138.0, 157.0, 165.4 ppm; IR (KBr): $\tilde{\nu} = 3187$, 1744, 1094 cm^{-1}; MS (CI): *m*/*z* (%): 233 (10) $[M+H]^+$, 205 (100), 113 (11); elemental analysis calcd (%) for $C_{12}H_{12}N_2O_3$: C 62.06, H 5.21, N 12.06; found C 61.69, H 5.08, N 12.16.

(3*R*)-3-[(*R*)-(5-Phenyl-oxazolidin-1-yl-2-one)]azetidin-2-one (3*R*)-34: This compound was prepared from (3*R*)-**14e**, flash chromatography (DCM/MeOH 30:1) providing crystalline (3*R*)-**34** (52 mg, 75 %). $[\alpha]_D^{22} = -77.8$ ($c = 1.1$ in MeOH); MS (CI): *m*/*z* (%): 233 (8) $[M+H]^+$, 205 (100), 113 (12); HRMS: *m*/*z*: calcd for $C_{12}H_{12}N_2O_3$: 233.0926; found: 233.0930. The rest of spectral and analytical data were in agreement with those described before for (3*S*)-**34**.

(3*S*)-3-(*N*-Benzyl-*N*-benzyloxycarbonylamino)azetidin-2-one [(3*S*)-35]: This compound was prepared from (3*S*)-**17f**, flash chromatography (toluene/acetone 7:1) providing (3*S*)-**35** (76 mg, 82 %) as an oil. The spectral and analytical data were in agreement with literature data: $[\alpha]_D^{22} = -8.8$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 90 °C): $\delta = 3.14$ (dd, $J = 2.9$, 5.5 Hz, 1H), 3.31 (t, $J = 5.5$ Hz, 1H), 4.49 (d, $J = 15.9$ Hz, 1H), 4.61 (d, $J = 15.9$ Hz, 1H), 4.90 (dd, $J = 2.9$, 3.5 Hz, 1H), 5.12 (d, $J = 12.6$ Hz, 1H), 5.16 (d, $J = 12.6$ Hz, 1H), 7.40 (br s, 1H), 7.22–7.34 ppm (m, 10H); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 90 °C): $\delta = 47.0$, 55.6, 70.2, 72.2, 132.2, 132.3, 132.7, 132.9, 133.4, 141.0, 143.5, 160.5, 172.0 ppm; IR (KBr): $\tilde{\nu} = 3299$, 1771, 1708 cm^{-1}; MS (CI): *m*/*z* (%): 311 (68) $[M+H]^+$,

283 (6), 239 (7), 221 (5), 91 (100); elemental analysis calcd (%) for $C_{18}H_{18}N_2O_3$: C 69.66, H 5.85, N 9.03; found C 69.59, H 6.19, N 9.11.

(3*R*)-3-(*N*-Benzyl-*N*-benzyloxycarbonylamino)azetidin-2-one [(3*R*)-35]: This compound was prepared from (3*R*)-**17e**, flash chromatography (toluene/acetone 7:1) providing (3*R*)-**35** (77 mg, 83%) as an oil. $[\alpha]_D^{22} = +8.0$ ($c = 1$ in CH_2Cl_2). The rest of the spectral and analytical data were in agreement with those described for (3*S*)-**35**. The same product was obtained in 83% yield from (3*R*)-**17g** with use of MMPP·6 H_2O (99 mg, 0.17 mmol), and had identical characterization data.

(3*R*,4*S*)-3-Benzyloxy-4-pentylazetidin-2-one [(3*R*,4*S*)-36]: This compound was prepared from (3*R*,4*S*)-**23e**, flash chromatography (toluene/EA 3:1) providing crystalline (3*R*,4*S*)-**36** (58 mg, 78%). M.p. 38–40 °C; $[\alpha]_D^{25} = +28.9$ ($c = 1.1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 6.6$ Hz, 3H), 1.25–1.57 (m, 6H), 1.60–1.71 (m, 2H), 3.38–3.74 (m, 1H), 4.67 (d, $J = 4.8$ Hz, 1H), 4.68 (d, $J = 11.9$ Hz, 1H), 4.86 (d, $J = 11.9$ Hz, 1H), 6.12 (brs, 1H), 7.27–7.38 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.8, 22.3, 25.5, 29.8, 31.5, 55.0, 72.7, 82.3, 127.6, 127.7, 128.3, 137.1, 168.8$ ppm; IR (KBr): $\tilde{\nu} = 1762, 1390, 1099$ cm^{-1}; MS (CI): *m*/*z* (%): 248 (100) $[M+H]^+$, 220 (30), 91 (74); elemental analysis calcd (%) for $C_{15}H_{21}NO_2$: C 72.84, H 8.55, N 5.66; found C 72.86, H 8.87, N 5.58.

(3*R*,4*S*)-3-Benzyloxy-4-isobutylazetidin-2-one [(3*R*,4*S*)-37]: This compound was prepared from (3*R*,4*S*)-**24e**, flash chromatography (toluene/EA 3:1) providing crystalline (3*R*,4*S*)-**37** (63 mg, 91%). M.p. 73–75 °C; $[\alpha]_D^{22} = +33.4$ ($c = 0.9$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.92$ (d, $J = 6.5$ Hz, 3H), 0.95 (d, $J = 6.5$ Hz, 3H), 1.50–1.57 (m, 2H), 1.59–1.74 (m, 1H), 3.81 (dt, $J = 4.9, 8.2$ Hz, 1H), 4.68 (dd, $J = 2.6, 4.9$ Hz, 1H), 4.68 (d, $J = 11.8$ Hz, 1H), 4.84 (d, $J = 11.8$ Hz, 1H), 6.35 (brs, 1H), 7.27–7.38 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.9, 23.1, 25.4, 38.5, 53.4, 72.7, 82.4, 127.7, 127.8, 128.3, 137.1, 168.9$ ppm; IR (KBr): $\tilde{\nu} = 1759, 1100, 1027$ cm^{-1}; MS (CI): *m*/*z* (%): 234 (100), $[M+H]^+$, 206 (48), 91 (91); elemental analysis calcd (%) for $C_{14}H_{19}NO_2$: C 72.07, H 8.21, N 6.00; found C 71.97, H 8.43, N 6.06.

Compound (3*R*,4*S*)-**37** was also obtained, in 84% yield and with identical characterization data, from (3*R*,4*S*)-**24g**, by use of MMPP·6 H_2O (99 mg, 0.17 mmol).

(3*R*,4*S*)-3-Benzyloxy-4-phenylethylazetidin-2-one [(3*R*,4*S*)-38]: This compound was prepared from (3*R*,4*S*)-**25e**, flash chromatography (toluene/EA 3:1) providing crystalline (3*R*,4*S*)-**38** (73 mg, 87%). M.p. 104–106 °C; $[\alpha]_D^{25} = +19.9$ ($c = 1.2$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.90–2.10$ (m, 2H), 2.62–2.79 (m, 2H), 3.74 (td, $J = 4.9, 8.1$ Hz, 1H), 4.69 (dd, $J = 2.6, 4.9$ Hz, 1H), 4.69 (d, $J = 11.8$ Hz, 1H), 4.88 (d, $J = 11.8$ Hz, 1H), 5.96 (brs, 1H), 7.15–7.52 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 31.7, 32.5, 54.4, 72.8, 82.4, 127.7, 127.8, 128.2, 128.3, 128.5, 137.1, 140.9, 168.5$ ppm; IR (KBr): $\tilde{\nu} = 1725, 1101, 1034$ cm^{-1}; MS (CI): *m*/*z* (%): 282 (100) $[M+H]^+$, 254 (66), 91 (81); elemental analysis calcd (%) for $C_{18}H_{20}NO_2$: C 76.84, H 6.81, N 4.98; found C 76.75, H 6.95, N 5.08.

Compound (3*R*,4*S*)-**38** was also obtained, in 84% yield and with identical characterization data, from (3*R*,4*S*)-**25g**, by use of MMPP·6 H_2O (99 mg, 0.17 mmol).

(3*R*,4*S*)-3-Benzyloxy-4-isopropylazetidin-2-one [(3*R*,4*S*)-39]: This compound was prepared from (3*R*,4*S*)-**26e**, flash chromatography (toluene/EA 3:1) providing crystalline (3*R*,4*S*)-**39** (58 mg, 88%): M.p. 85–86 °C; $[\alpha]_D^{26} = +120.4$ ($c = 1.1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 3H), 1.9–2.1 (m, 1H), 3.35 (dd, $J = 4.9, 9.2$ Hz, 1H), 4.67 (dd, $J = 2.9, 4.9$ Hz, 1H), 4.72 (d, $J = 11.9$ Hz, 1H), 4.94 (d, $J = 11.9$ Hz, 1H), 6.41 (brs, 1H), 7.2–7.4 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.8, 18.9, 28.0, 60.8, 72.5, 81.9, 127.5, 127.6, 128.3, 137.3, 169.3$ ppm; IR (film): $\tilde{\nu} = 3262, 1760$ cm^{-1}; MS (CI): *m*/*z* (%): 220 (60) $[M+H]^+$, 192 (21), 91 (100); elemental analysis calcd (%) for $C_{13}H_{17}NO_2$: C 71.20, H 7.81, N 6.39; found C 71.16, H 8.00, N 6.46.

The same product was also obtained, in 91% yield and with identical characterization data, from (3*R*,4*S*)-**26g**, by use of MMPP·6 H_2O (99 mg, 0.17 mmol).

(3*R*,4*S*)-3-Benzyloxy-4-phenylazetidin-2-one [(3*R*,4*S*)-40]: This compound was prepared from (3*R*,4*S*)-**27e**, flash chromatography (toluene/EA 3:1) providing crystalline (3*R*,4*S*)-**40** (73 mg, 96%). M.p. 207–210 °C; $[\alpha]_D^{25} = +96.8$ ($c = 1$ in DMSO); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.09$ (d, $J = 11.1$ Hz, 1H), 4.26 (d, $J = 11.1$ Hz, 1H), 4.87 (d, $J = 4.5$ Hz, 1H), 4.94 (dd, $J = 2.3, 4.5$ Hz, 1H), 8.65 (brs, 1H), 6.83–6.86 (m, 2H), 7.18–7.21 (m, 2H), 7.31–7.39 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 56.7, 71.0, 81.7, 127.6, 127.8, 128.1, 136.9, 137.3, 167.3$ ppm; IR (KBr): $\tilde{\nu} = 1724, 1123, 1028$ cm^{-1}; MS (CI): *m*/*z* (%): 254 (100), $[M+H]^+$, 162 (29), 91 (91); elemental analysis calcd (%) for $C_{16}H_{15}NO_2$: C 75.87, H 5.97, N 5.53; found C 75.77, H 5.94, N 5.88.

Compound (3*R*,4*S*)-**40** was also obtained, in 95% yield and with identical characterization data, from (3*R*,4*S*)-**27g**, by use of MMPP·6 H_2O (99 mg, 0.17 mmol).

(3*R*,4*S*)-3-Hydroxy-4-phenylazetidin-2-one [(3*R*,4*S*)-41]: A catalytic amount of Pd/C (10%) was added to a solution of β-lactam (3*R*,4*S*)-**40** (126 mg, 0.5 mmol) in MeOH/dioxane (1:1, 8 mL) and the mixture was hydrogenated at atmospheric pressure until the starting β-lactam had been consumed (ca. 24 h). The catalyst was filtered off and washed with MeOH, and the solution was evaporated. Flash chromatography (DCM/MeOH 20:1) gave crystalline (3*R*,4*S*)-**41** (59 mg, 72%); $[\alpha]_D^{25} = +181.9$ ($c = 1.5$ in MeOH). Spectral and analytical data were in good agreement with literature data.[56]

(3*R*,4*S*)-3-Hydroxy-4-isobutylazetidin-2-one [(3*R*,4*S*)-43]: A catalytic amount of Pd/C (10%) was added to a solution of β-lactam (3*R*,4*S*)-**37** (117 mg, 0.5 mmol) in MeOH (4 mL) and the mixture was hydrogenated at atmospheric pressure until the starting β-lactam had been consumed (ca. 24 h). The catalyst was filtered and washed with MeOH, and the solution was evaporated. Flash chromatography (DCM/MeOH 20:1) gave crystalline (3*R*,4*S*)-**43** (61 mg, 85%). M.p. 123–127 °C; $[\alpha]_D^{20} = +28.0$ ($c = 1$ in MeOH); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 0.94$ (d, $J = 6.7$ Hz, 3H), 0.97 (d, $J = 6.5$ Hz, 3H), 1.40–1.54 (m, 2H), 1.64–1.75 (m, 1H), 3.75 (ddd, $J = 4.8, 5.8, 8.0$ Hz, 1H), 4.79 ppm (d, $J = 4.8$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 25.0, 26.0, 28.9, 42.3, 57.8, 80.0, 175.6$ ppm; IR (KBr): $\tilde{\nu} = 1681, 1418, 1097, 1033$ cm^{-1}; MS (CI): *m*/*z* (%): 144 (100), $[M+H]^+$, 126 (16), 99 (16); elemental analysis calcd (%) for $C_7H_{13}NO_2$: C 58.72, H 9.15, N 9.78; found C 58.89, H 9.38, N 9.89.

(2*R*,3*S*)-3-Amino-2-hydroxy-5-methylhexanoic acid [(2*R*,3*S*)-45]: Compound (3*R*,4*S*)-**43** (29 mg, 0.2 mmol) was dissolved in HCl (6 N, 0.8 mL) and stirred for 4 h. The reaction mixture was concentrated to give crystalline (2*R*,3*S*)-**44** (39 mg, 99%). ^{1}H NMR (300 MHz, CD_3OD): $\delta = 0.97$ (d, $J = 6.3$ Hz, 3H), 0.98 (d, $J = 6.3$ Hz, 3H), 1.46–1.55 (m, 1H), 1.61–1.80 (m, 2H), 3.51–3.58 (m, 1H), 4.23 ppm (d, $J = 3.1$ Hz, 1H); ^{1}H NMR (300 MHz, D_2O): $\delta = 0.87$ (d, $J = 6.1$ Hz, 3H), 0.88 (d, $J = 6.1$ Hz, 3H), 1.42–1.69 (m, 3H), 3.60–3.65 (m, 1H), 4.34 ppm (d, $J = 3.2$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 20.8, 20.9, 23.6, 38.0, 51.1, 68.6, 172.7$ ppm. Treatment of (2*R*,3*S*)-**44** with Dowex 50W×8 gave β-amino-α-hydroxy acid (2*R*,3*S*)-**45** in quantitative yield. $[\alpha]_D^{25} = +25.2$ ($c = 0.6$ in AcOH). Spectral and analytical data were in good agreement with literature data.[61]

(3*R*)-3-Hydroxy-1-[(2*S*)-2-(1-ethyl-1-methoxypropyl)pyrrolidin-1-yl]azetidin-2-one [(3*R*)-46]: A catalytic amount of Pd/C (10%) was added to a solution of (3*R*)-**4e** (346 mg, 1 mmol) in MeOH (13 mL), and the mixture was hydrogenated at atmospheric pressure until the starting β-lactam had been consumed (ca. 24 h). The catalyst was filtered and washed with MeOH, and the solution was evaporated. Flash chromatography (Et_2O/PE 9:1) gave (3*R*)-**46** (251 mg, 98%) as an oil. $[\alpha]_D^{30} = +19.6$ ($c = 1.1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 7.5$ Hz, 3H), 0.87 (t, $J = 7.5$ Hz, 3H), 1.47–1.60 (m, 2H), 1.62–1.72 (m, 2H), 1.75–1.93 (m, 4H), 2.89–2.94 (m, 1H), 3.13–3.18 (m, 1H), 3.28 (s, 3H), 3.28–3.30 (m, 1H), 3.33 (dd, $J = 1.6, 5.0$ Hz, 1H), 3.61 (t, $J = 5.0$ Hz, 1H), 4.45 (s, 1H), 4.69 ppm (dd, $J = 1.6, 5.0$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 7.9, 8.3, 23.3, 23.4, 25.5, 26.3, 48.3, 50.2, 54.1, 66.4, 71.3, 79.5, 168.0$ ppm; IR (KBr): $\tilde{\nu} = 3300, 1760$ cm^{-1}; MS (EI): *m*/*z* (%): 256 (2) $[M]^+$, 155 (100), 127 (25), 101 (27); elemental analysis calcd (%) for $C_{13}H_{24}N_2O_3$: C 60.91, H 9.44, N 10.93; found C 61.05, H 9.68, N 10.69.

***p*-Nitrobenzoate [(3*R*)-47]**: A solution of (3*R*)-**46** (128 mg, 0.5 mmol), *p*-nitrobenzoyl chloride (142 mg, 0.75 mmol), and TEA (0.42 mL, 3 mmol) in DCM (5 mL) was stirred at rt for 3 h. The reaction mixture was washed with water (1×7 mL), diluted HCl (2×7 mL), saturated $NaHCO_3$ (1×7 mL), and brine (1×7 mL). The organic layer was dried (sodium sulfate), filtered, and evaporated. Flash chromatography (Et_2O/PE 1:1) gave crystalline (3*R*)-**47** (193 mg, 95%). M.p. 89–91 °C; $[\alpha]_D^{24} = +0.6$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 7.6$ Hz, 3H),

0.92 (t, J = 7.6 Hz, 3H), 1.57–1.67 (m, 2H), 1.69–1.75 (m, 2H), 1.76–1.86 (m, 3H), 1.88–1.98 (m, 1H), 2.96–3.04 (m, 1H), 3.22–3.24 (m, 1H), 3.26 (s, 3H), 3.34–3.39 (m, 1H), 3.48 (dd, J = 1.8, 5.8 Hz, 1H), 3.88 (dd, J = 4.8, 5.8 Hz, 1H), 5.63 (dd, J = 1.8, 4.7 Hz, 1H), 8.24 (d, J = 9 Hz, 2H), 8.30 ppm (d, J = 9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.9, 8.7, 23.0, 24.0, 25.6, 26.2, 47.4, 50.0, 54.1, 66.6, 72.8, 123.0, 131.0, 134.0, 151.0, 163.0, 164.0 ppm; IR (KBr): $\tilde{\nu}$ = 1778, 1733, 1540, 1270 cm^{-1}; MS (EI): m/z (%): 405 (1) $[M]^+$, 304 (100), 101 (33); elemental analysis calcd (%) for $C_{20}H_{27}N_3O_6$: C 59.25, H 6.71, N 10.36; found C 59.06, H 6.56, N 10.55.

(3*S*)-3-*tert*-Butoxycarbonylaminoazetidin-2-one [(3*S*)-48]: A catalytic amount of Pd/C (10%) was added to a solution of (3*S*)-**35** (93 mg, 0.3 mmol) in MeOH (10 mL), and the mixture was hydrogenated at 6 atm and rt. After 48 h, the catalyst was filtered off and washed with MeOH, and the solution was evaporated. The residue was dissolved in MeOH (3 mL), and Boc_2O (169 mg, 0.75 mmol), TEA (0.12 mL, 0.9 mmol), and a catalytic amount of DMAP were added. Conventional workup and flash chromatography (DCM/MeOH 15:1) gave crystalline (3*S*)-**48** (34 mg, 60%). $[\alpha]_D^{20}$ = −20.1 (c = 0.8 in CH_3OH). Spectral and analytical data were in good agreement with literature data.[62]

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