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**Author(s):** Jäger, Christina; Nieger, Martin; Rissanen, Kari; Deska, Jan

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# Multienzymatic Synthesis of $\gamma$ -Lactam Building Blocks from Unsaturated Esters and Hydroxylamine

Christina Jäger,<sup>[a]</sup> Martin Nieger,<sup>[a]</sup> Kari Rissanen,<sup>[b]</sup> and Jan Deska<sup>\*[a]</sup>

The assembly of enzymatic cascades and multi-step reaction sequences represents an attractive alternative to traditional synthetic-organic approaches. The biocatalytic reaction mediators offer not only mild conditions and permit the use of environmentally benign reagents, but the high compatibility of different enzymes promises more streamlined reaction setups. In this study, a triple-enzymatic strategy was developed that enables the direct conversion of  $\gamma,\delta$ -unsaturated esters to *N*-hydroxy- $\gamma$ -lactam building blocks. Hereby, a lipase-catalyzed

hydroxylaminolysis generates hydroxamic acid intermediates that are subsequently aerobically activated by horseradish peroxidase and glucose oxidase to cyclize in an intramolecular nitroso ene reaction. Utilizing the hydroxylaminolysis/ene-cyclization sequence for the preparation of an aza-spirocyclic lactam, the multi-enzymatic methodology was successfully employed in the synthesis of key intermediates en route to alkaloids of the *Cephalotaxus* family.

## Introduction

The N-heterocyclic motif is omnipresent across a wide range of bioactive compounds and flexible synthetic methodologies to incorporate nitrogen into complex molecular frameworks represent an indispensable part in the modern synthetic-organic toolbox. Biocatalytic transformations, for all kinds of purposes, have been attracting more and more attention in the last years also by the synthetic-organic community. And at the same time that chemists started to familiarize with enzymes as catalysts in general, the interest for non-natural activities of enzymes has been rising exponentially. Nowadays, in addition to the more traditional biocatalytic methods to form the synthetically relevant C–N bonds through reductive aminations,<sup>[1]</sup> the first examples for new-to-nature reactivities such as carbene and nitrene insertions have been established.<sup>[2]</sup> Nitroso ene reactions, first explored in the 1960's,<sup>[3]</sup> are an elegant method for the construction of new C–N functionalities and as such, have been utilized in the synthesis of a range of

complex bioactive molecules.<sup>[4]</sup> Such transformations include highly reactive nitrosocarbonyl species, which are mostly engaging as “super-enophile”. The origin of their high reactivity can be found in an energetically low-lying LUMO that allows for a broad application spectrum.<sup>[5]</sup> Several *in situ* methods to produce nitroso compounds were developed over the course of time, but the oxidation of hydroxamic acids is one of the prime methods. The dehydrogenation of hydroxamic acids can either be achieved by stoichiometric oxidants or through transition metal catalysis using simpler electron acceptors such as hydrogen peroxide.<sup>[6–8]</sup> We have recently developed a first, generally applicable, biocatalytic methodology with applications in both nitroso ene and Diels-Alder-type transformations. The enzyme-based system relies on the interplay of horseradish peroxidase (HRP) as oxidizer of the N–O substrates with glucose oxidase (GOx) as activator of aerial oxygen under consumption of D-glucose. The thus formed nitrosocarbonyl species readily undergo non-enzymatic C–N coupling reactions with olefinic and diene moieties in inter- or intramolecular fashion to deliver a range of N-heterocyclic molecular architectures.<sup>[9,10]</sup> In addition to the wide scope, the robust system was proven to be highly scalable and recyclable, therefore allowing higher yields while improving atom economy.<sup>[10]</sup> In continuation of the enzyme-driven incorporation of nitrogen into heterocyclic building blocks, we envisaged that we could use an extended biocatalytic sequence to introduce the key nitrogen atom from a basic inorganic reagent such as hydroxylamine (Scheme 1).

Here, we report on the development of a fully biocatalytic two-step approach to five-membered N-heterocycles that combines the previously discovered enzymatic nitroso ene reaction with a lipase-mediated formation of hydroxamic acids, the key intermediates for the peroxidase activation. Starting from readily available  $\gamma,\delta$ -unsaturated esters and aqueous hydroxylamine, the enzyme-driven sequence provides a convenient and scalable access to olefin-functionalized  $\gamma$ -lactam building blocks, and its utility is illustrated through chemo-

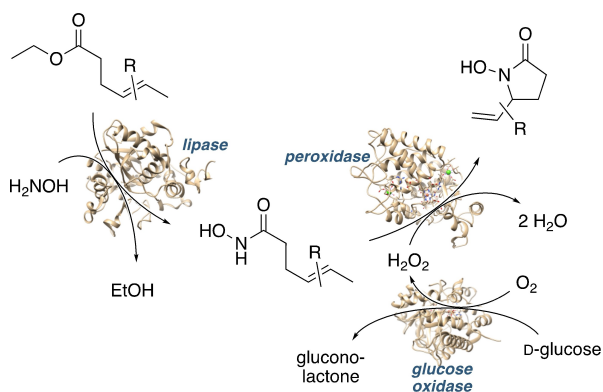
[a] C. Jäger, Dr. M. Nieger, Prof. Dr. J. Deska  
Department of Chemistry  
University of Helsinki  
A.I. Virtasen aukio 1  
00560 Helsinki (Finland)  
E-mail: jan.deska@helsinki.fi  
Homepage: www.deskalab.com

[b] Prof. K. Rissanen  
Department of Chemistry  
University of Jyväskylä  
P.O. Box 35, 40014 Jyväskylä (Finland)

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**Scheme 1.** Intended biocatalytic sequence for the preparation of N-heterocycles using hydroxylamine as nitrogen source.

enzymatic formal total synthesis of the tetracyclic alkaloid cephalotaxine.

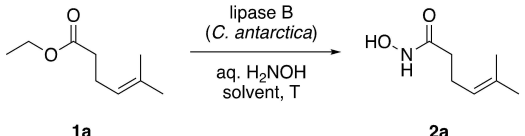
## Results and Discussion

Since traditional chemical reactants and catalysts are often suffering from limited compatibility with each other, enzymes represent an attractive alternative as proteinogenic reaction mediators are naturally optimized to work under such circumstances, in presence of a plethora of other biopolymers and small molecule metabolites. The design of cascade reactions based on enzymatic transformations, resembling a miniaturized artificial metabolism, has therefore become a prominent scientific target with applications in a number of optimized synthetic routes to complex natural products and active pharmaceutical ingredients.<sup>[11]</sup> Particularly the reduction of individual reaction and purification steps, and as a consequence the improved waste and energy profile, can be seen as reason

why these multi-enzymatic approaches have quickly been moved from fundamental academic studies to industrial implementations.<sup>[12,13]</sup>

While the nitroso ene reaction of *N*-hydroxycarbamates and hydroxamic acids by means of enzyme catalysts had recently already been studied by us in much detail, a fully biocatalytic sequence starting from unsaturated esters would still require the development of an enzyme-mediated hydroxylaminolysis to directly access the necessary nitroso precursors. Direct hydroxylaminolysis of esters to yield hydroxamic acids is usually performed with a large excess of hydroxylamine, either in presence of strong bases but sometimes also in combination with catalytic additives to accelerate the reaction.<sup>[14]</sup> While lipases are mostly used for the production of enantiopure alcohols or esters via kinetic resolutions<sup>[15]</sup> or desymmetrizations,<sup>[16]</sup> these extraordinarily robust biocatalysts evolved naturally for the conversion of triglycerides where fatty acids can be trapped with different kinds of nucleophiles. In addition to the more common hydrolytic, aminolytic and alcoholic transformations, also hydroxylamine was found to act as reaction partner in the lipase-mediated transfer of fatty acid esters giving rise to the corresponding hydroxamic acids.<sup>[17,18]</sup> In search for hydroxylaminolysis protocols that would serve our intended cascade design, we were delighted to find that the conditions originally developed for the transformation of fatty acid esters using *Candida antarctica* lipase B (CALB)<sup>[18]</sup> were also effectively converting ethyl ester **1a** at 40 °C in dioxane after which the hydroxamic acid **2a** was obtained in 72% yield (Table 1, entry 1). Adjusting the reaction conditions for the subsequent application in a potential cascade reaction, the substrate loading was slightly decreased to match reaction volumes and concentration typical for the HRP/GOx-catalyzed nitroso-ene cyclization. This improved the hydroxylaminolysis significantly with a yield of **2a** of 98% and a reduced reaction time of 11 h (Table 1, entry 2). When the reaction was slightly heated to 50 °C, full conversion of substrate **1a** was observed

**Table 1.** Reaction optimization for the lipase-catalyzed hydroxylaminolysis of model ester **1a**.

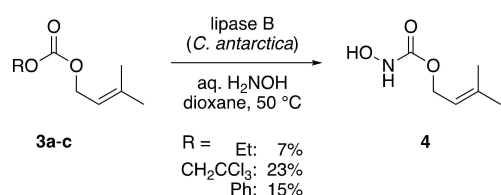
						
#	ester <b>1a</b> [M]	H <sub>2</sub> NOH [M]	solvent	T [°C]	t [h]	Yield <sup>[a]</sup> [%]
1	0.4	0.5	dioxane	40	48	72
2	0.14	0.5	dioxane	40	11	98
3	0.14	0.5	dioxane	50	5	98
4 <sup>[b]</sup>	0.14	0.5	dioxane	50	5	0
5	0.14	0.25	dioxane	50	48	98
6	0.14	0.14	dioxane	50	72	0 <sup>[c]</sup>
7	0.14	0.5	<i>n</i> -heptane	50	4	0 <sup>[c]</sup>

Reaction conditions: **1a** and H<sub>2</sub>NOH (50 w% in water) were dissolved in dioxane. 5 mg lipase CALB immo plus was added and the reaction was heated. After full conversion was reached, the reaction was filtered through a short silica plug (EtOAc). [a] <sup>1</sup>H NMR yields, dimethylsulfone as internal standard. [b] no lipase added. [c] Conversion < 5%.

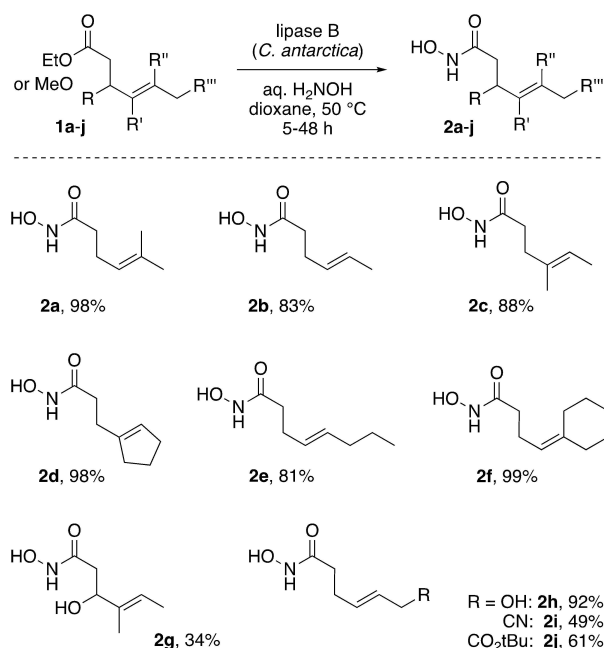
already after 5 h by maintaining 98% yield of the product **2a** (Table 1, entry 3). Since common procedures yield hydroxylaminolysis by adding excess of  $\text{H}_2\text{NOH}$ , the reaction was also subjected to the same conditions by omitting the lipase. Yet, no conversion could be observed after 5 h (Table 1, entry 4), confirming the necessity of CALB as catalyst in this reaction. While the reduction of the hydroxylamine equivalents from 3.6 to 1.8 resulted in a significantly increased reaction time, **2a** was still obtained in an excellent yield of 98% (Table 1, entry 5). In contrast, further reduction to only an equimolar amount of the N-nucleophile reduced the conversion to a minimum (Table 1, entry 6). Additionally, *n*-heptane was tested as an alternative biphasic solvent system (Table 1, entry 7). Also here, no conversion was observed, strongly suggesting that only water miscible solvents are applicable. As shorter reaction times in the range of 5 h are certainly more convenient, the conditions of entry 3 were chosen for further testing and scope studies.

Since our original studies on peroxidase-induced nitroso ene and nitroso Diels-Alder cycloadditions focused on *N*-hydroxy carbamates as main substrate family, we next attempted to extend the methodology also to the structurally closely related ethyl prenyl carbonate **3a**. Yet, when applying the CALB-catalyzed procedure for the hydroxylaminolysis, only a poor yield of 7% of the *N*-hydroxy carbamate **4** was obtained (Scheme 2). By altering the substitution pattern in the unsymmetric carbonates, a minor improvement could be achieved with trichloroethanol and phenol as leaving groups. It is generally known that lipases can activate either side of a carbonate, e.g. in the synthesis of glycerol carbonate or other cyclic carbonates,<sup>[19,20]</sup> and a certain regioselectivity ("olefin effect") was found in the hydrolysis of unsymmetric diesters.<sup>[21]</sup> In our case, however, no synthetically useful selectivity could be observed and significant amounts of prenyl alcohol, due to hydrolysis and decarboxylation of the resulting hemicarbonate, were detected.

On the other hand, variation of the substitution pattern of  $\gamma,\delta$ -unsaturated ethyl esters proved to be generally well tolerated and the hydroxylaminolysis method turned out to be applicable for a wide range of esters (Scheme 3). A range of analogues of model substrate **1a** were successfully converted, and the corresponding hydroxamic acids **2b-2j** were obtained in good to quantitative yields. When applying the 1,2-disubstituted olefins **1b** and **1e** as pure *trans*-isomer, no isomerization was observed and hydroxamic acids **2b** and **2e**, respectively, were obtained exclusively in *trans*-configuration. Cyclic patterns were also well accepted, with **1d** and **1f** giving rise to hydroxamic acids **2d** and **2f** in excellent yields. It is worth noting that a 10-fold scale-up in case of **1f** required an



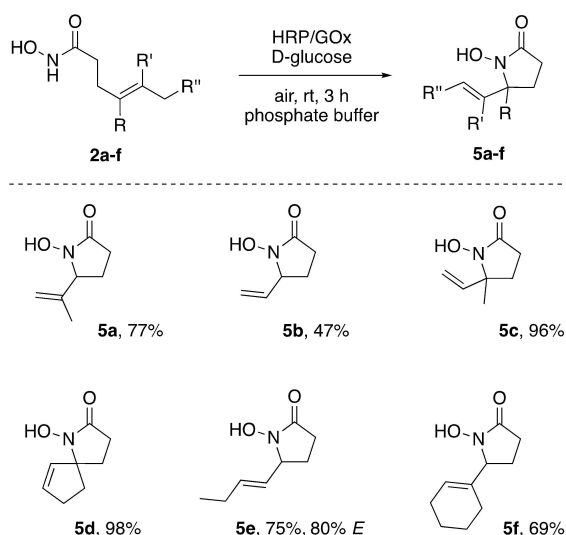
Scheme 2. Biocatalytic hydroxylaminolysis of unsymmetric carbonates.



Scheme 3. Scope of the biocatalytic hydroxylaminolysis.

extended reaction time of 24 h to reach completion, however, the product was still obtained in quantitative yield. Also important to point out, the enzymatic method utilizing *Candida antarctica* lipase B resulted in a similar or even better reaction outcome than the traditional chemical method employing large excess of hydroxylamine and base. Particularly for the hetero-functionalized substrates **1h-1j**, the hydroxylaminations proceeded significantly cleaner than the base-mediated counterpart and the base-induced migration of the olefinic double bond into conjugation to the electron-withdrawing groups could be entirely suppressed with the lipase-catalyzed protocol.

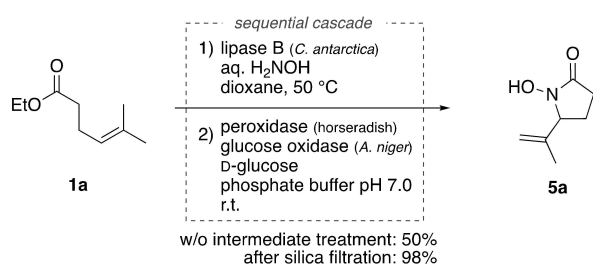
For the second step of our intended sequence, we could rely on the previously optimized protocol for the ene-type cyclization using glucose oxidase and horseradish peroxidase. Even though the method has previously been mainly applied to *N*-hydroxycarbamates as acylnitroso precursors, also all tested hydroxamic acids were well accepted by the peroxidase (Scheme 4). The corresponding  $\gamma$ -lactams were thus obtained at room temperature in aqueous solution while the traditional methods for the preparation of **5a** requires significantly higher temperatures.<sup>[22]</sup> The biocatalytic method accepted a range of different substitution patterns around the olefin, yielding products **5b**, **5c** and cyclic **5f** in moderate to excellent yields. In addition, the method was applied to hydroxamic acid **2d**, giving rise to the spirocyclic product **5d** in an excellent yield, which is substantially better than the purely chemical methods existing for this substrate.<sup>[23]</sup> When employing the *E*-isomer of hydroxamic acid **2e**, the product **5e** was obtained in a good yield of 75% and a *E/Z*-ratio of 4:1. Overall, both yields and *E/Z* selectivities were found to be in the same range as for their corresponding *N*-hydroxycarbamates, underlining the general applicability of the peroxidase-induced nitroso-ene cyclization. This together with its mild reaction conditions and commer-



**Scheme 4.** Scope of the biocatalytic nitroso-ene reaction of  $\gamma,\delta$ -unsaturated hydroxamic acids.

cially available catalysts makes it a promising and generic tool for further synthetic implementations. Unfortunately, the heterofunctionalized hydroxamic acids **2g–2i** could not be cyclized, and further optimization of the general method to also accommodate these synthetically attractive building blocks will be necessary in future studies.

With these promising results in hand, a cascade design was the next logical step (Scheme 5). After the hydroxylaminolysis of **1a** showed full conversion after 5 h, the immobilized CALB was removed through simple filtration of the polymer beads and the dioxane solution was added to the aqueous mixture containing the HRP/GOx couple. While the reaction time of this second step increased only slightly to 4 h, unfortunately, the overall yield after two steps dropped to 50%. Here, the remaining unreacted hydroxylamine in the solution with the hydroxamic acid was identified as the major issue. The nitroso-ene reaction was tested separately by deliberately adding hydroxylamine and a substantial decrease in conversion rates was observed. As equimolar amounts of the nitrogen nucleophile were insufficient to facilitate a complete hydroxylaminolysis in the initial step and thus a slight excess was unavoidable, several methods to trap the free hydroxylamine were tested. Yet, addition of acidic ion exchange resins or desiccants could not counter the undesired effect (Supplementary Table 1). On

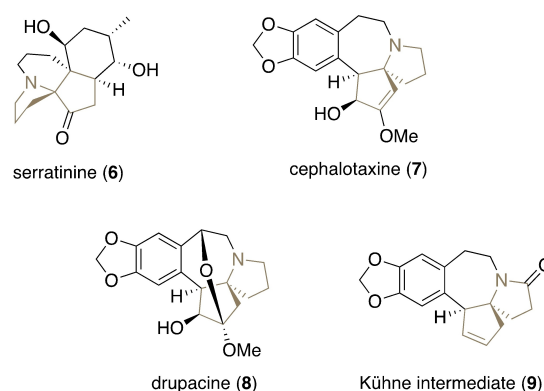


**Scheme 5.** Sequential cascade design combining a biocatalytic hydroxylaminolysis with an enzymatic nitroso-ene cyclization.

the other hand, when the hydroxylaminolysis solution was filtered through a short plug of silica, an excellent, almost quantitative yield was restored. Another future solution to this issue could be found in directed evolution to engineer a peroxidase/glucose oxidase couple which would exhibit a higher tolerance against hydroxylamine.

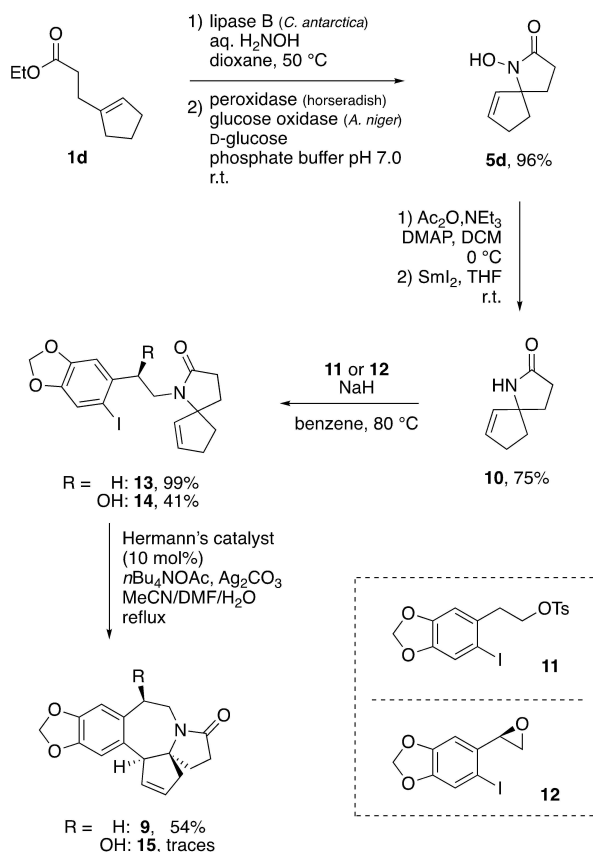
Within the ene-cyclization product scope, particularly the 1-azaspiro[4.4]nonane motif of **5d** stands out as attractive synthetic feature. The azaspirocyclic skeletons can be found as a unique structural feature in a variety of alkaloids which have traditionally played a role in folk medicine (Figure 1).<sup>[24]</sup> More in-depth studies revealed that a significant number of these phytopharmaceuticals exhibit attractive bioactivity features, ranging from selective cytotoxicity profiles over inflammatory properties to activities related to the treatment of Alzheimer's disease. Especially interesting are alkaloids from the *Cephalotaxus* family due to their activity against a variety of cancers that also proved effective when resistance towards other pharmaceuticals occurred.<sup>[25]</sup> In synthetic studies towards cephalotaxine-type alkaloids, the Kühne intermediate **9** with its tetracyclic core structure plays a crucial role and was therefore utilized in several total syntheses towards natural products from that compound class.<sup>[23,26]</sup>

The spirocycle **5d** represents the key building block en route to the Kühne intermediate **9**, and hence, we went on to evaluate the synthetic utility of the peroxidase-induced spirocyclization (Scheme 6). Thanks to the use of cheap commercial biocatalysts and a proven scalability, the enzymatic approach promised to give us an easy access to the azaspiro[4.4]nonane motif in substantial quantities. While the sequential cascade, similarly to the previous attempts with **1a**, only produced a mediocre yield of 41% of **5d** from ester **1d**, the two-step protocol worked smoothly and even after a tenfold scale-up, an excellent yield of the spirocycle **5d** of 97% (108 mg) was achieved. The subsequent conversion reduction of the N–O bond followed an established two-step protocol consisting of O-acetylation and reduction by  $\text{SmI}_2$ , which gave rise to amide **10** in 75% overall yield. In order to prepare for the Heck-based cyclization to the tetracyclic alkaloid structures, **10** was N-alkylated with two different iodinated benzodioxole handles. In addition to the direct route to the Kühne intermediate where trapping of the sodium amide with tosylate **11** provided **13**,



**Figure 1.** Alkaloids featuring the 1-azaspiro[4.4]nonane motif.





**Scheme 6.** Chemoenzymatic synthesis of cephalotaxine precursors through combination of a biocatalytic spirocyclization and palladium-mediated Heck cyclization.

replacement of **11** by epoxide **12** gave also rise to a hydroxylated variant (**14**) that would open up a route to oxygen-bridged cephalotaxine derivatives such as drupacine (**8**).<sup>[27]</sup> Unfortunately, the epoxide opening also led to almost equimolar amounts of an impurity that could not be chromatographically separated from **14**. The final metal-catalyzed cyclizations were conducted following established protocols for intramolecular Heck reactions.<sup>[23,26]</sup> Especially the addition of silver carbonate turned out to effectively prevented undesired isomerizations and Kühne intermediate **9** was thus obtained in 54% yield. So far, the Heck-type cyclization of **14** to give the hydroxy-modified Kühne intermediate **15** remained unsuccessful. Even though full conversions were achieved, no pure **15** could be isolated from the complex reaction mixtures, and further optimization of the palladium-catalyzed transformation will be required.

## Conclusions

A fully biocatalytic reaction sequence design was established that allows the direct generation of five-membered N-heterocycles from linear unsaturated esters. Combining the lipase-catalyzed hydroxylaminolysis with a subsequent peroxidase-induced ene-type cyclization, high overall yields under mild

reaction conditions were achieved. Here, *Candida antarctica* lipase B is utilized to generate hydroxamic acids which serve as precursor for highly reactive acylnitroso species that are formed through dehydrogenation by horseradish peroxidase, with glucose oxidase providing the necessary hydrogen peroxide from air as terminal oxidant. Utilizing a sequence that is only reliant on robust and commercially available enzyme catalysts, a spirocyclic gamma-lactam could be prepared in synthetically useful quantities, allowing for the chemoenzymatic formal total synthesis of cephalotaxine via the previously established Kühne intermediate.

## Experimental Section

**General methods & materials:** Commercially available reagents were used without further purification. glucose oxidase (lyophilized powder, type II, 158200 U/g, *Aspergillus niger*) and horseradish peroxidase (lyophilized powder, beige, 173 U/mg) were obtained from Sigma Aldrich. Lipase CALB immo plus was obtained from c-LEcta. All reactions were carried out under argon atmosphere and performed with dry solvents if not stated differently. All enzymatic reactions were carried out under non-inert conditions. Esters **1a–1f** were synthesized on literature protocols.<sup>[26,28]</sup> Solvents were dried with the help of a VAC Solvent Purification System. Silica gel from Merck (Millipore 60, 40–60 µm, 240–400 mesh) was used for column chromatography and silica pad filtrations. Reactions were monitored via thin layer chromatography (TLC) using precoated silica gel plates from Macherey-Nagel (TLC Silica gel 60 F<sub>254</sub>). The spots were identified using irradiation with UV-light and a staining solution (basic KMnO<sub>4</sub> solution). <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured with a Bruker Avance NEO 400 at 20 °C. The chemical shifts are reported in ppm related to the signal of residual solvent of CDCl<sub>3</sub> (<sup>1</sup>H: (CDCl<sub>3</sub>) = 7.26 ppm, <sup>13</sup>C: (CDCl<sub>3</sub>) = 77.2 ppm). Infrared spectra were recorded as thin film on a Bruker ALPHA ATR FT-IR device. High resolution mass spectrometry was performed on a Jeol JMS 700 spectrometer. HPLC measurements were performed at a n Agilent 1100 system with a G1362 A binary pump and G1315B diode array detector using a Daicel Chiralpak IA column; method: 40% iPrOH in n-hexane, 1.0 mL/min.

**Representative protocol for the enzymatic hydroxyaminolysis: 3-(Cyclopent-1-en-1-yl)-N-hydroxypropanamide (2d)** Aqueous hydroxylamine (0.15 mL, 50% w/w in H<sub>2</sub>O) and *Candida antarctica* lipase B (50 mg) were added to a 0.14 M solution of ester **1a** (118 mg, 0.70 mmol) in 1,4-dioxane (5 mL), and the reaction was incubated at 50 °C. Full conversion was reached after 24 h. The reaction mixture was filtered through a silica plug (EtOAc) and the solvent was removed under reduced pressure. The crude was purified via silica pad filtration (EtOAc) to yield **2d** as a beige solid (107 mg, 0.69 mmol, 98%). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 8.54 (bs, 2H, -NH-, -OH), 5.06 (t, J = 6.7 Hz, 1H), 2.32 (q, J = 7.0 Hz, 2H), 2.18 (t, J = 7.2 Hz, 2H), 1.69 (s, 3H), 1.61 (s, 3H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ 171.3, 134.1, 121.9, 33.2, 25.7, 23.8, 17.7. FT-IR (ATR) ν [cm<sup>-1</sup>] = 3200 (m), 2910 (m), 1624 (vs), 1539 (s), 1067 (s). Spectral data are in agreement with literature reports.<sup>[29]</sup>

**Representative protocol for the enzymatic nitroso-ene reaction: 1-Hydroxy-1-azaspiro[4.4]non-6-en-2-one (5a)** To a 10 mM solution of hydroxamic acid **2d** (108 mg, 0.70 mmol) in 63 mL phosphate buffer (100 mM, pH 7.0) and 7 mL dioxane was added 1.4 kU HRP and 1.4 kU GOx. The reaction was initiated by addition of D-glucose (631 mg, 3.5 mmol) and incubated at room temperature. Full conversion was reached after 4.5 h and the reaction mixture was extracted three times with EtOAc. The combined

organic phases were dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent was removed under reduced pressure. The crude was purified via column chromatography on silica gel (DCM + 5% MeOH + 1%  $\text{NEt}_3$ ,  $R_f$  = 0.34 (DCM + 5% MeOH)) to yield **5d** as white solid (104 mg, 0.68 mmol, 97%).  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.44 (bs, 1H, -OH), 5.00 (d,  $J$  = 15.5 Hz, 2H), 4.28 (dd,  $J$  = 8.4, 5.6 Hz, 1H), 2.51–2.31 (m, 2H), 2.29–2.16 (m, 1H), 1.86–1.75 (m, 1H), 1.73 (s, 3H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  142.4, 114.2, 65.0, 27.2, 21.5, 16.9. FT-IR (ATR)  $\nu$  [ $\text{cm}^{-1}$ ] = 3085 (vw), 2497 (w), 1668 (s), 1456 (m), 926 (s). Spectral data are in agreement with literature reports.<sup>[30]</sup>

## Supporting Information

Experimental procedures and analytical data that support the findings of this study are available in the supplementary material of this article. Additional references are cited within the Supporting Information.<sup>[31–42]</sup> Primary data from this study are freely available at Zenodo.<sup>[43]</sup>

Deposition Number(s) 2282061 (for **12**) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** biocatalysis • ene reaction • enzyme cascades • heterocycles • hydroxylaminolysis

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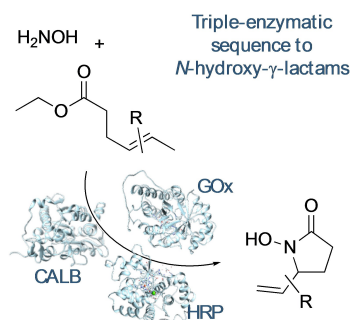
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## RESEARCH ARTICLE

*N*-hydroxy- $\gamma$ -lactams are produced through an enzymatic sequence combining a lipase-catalyzed hydroxylamidation with an oxidase/peroxidase-induced ene-type cyclization. This methodology provides a mild and scalable access to *N*-heterocyclic building blocks from basic  $\gamma,\delta$ -unsaturated esters and aqueous hydroxylamine, and its utility is illustrated by the formal total synthesis of the tetracyclic alkaloid cephalotaxine.



*C. Jäger, Dr. M. Nieger, Prof. K. Rissanen, Prof. Dr. J. Deska\**

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**Multienzymatic Synthesis of  $\gamma$ -Lactam Building Blocks from Unsaturated Esters and Hydroxylamine**

