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Novel Large-Ring 1,3-Bridged 2-Azetidinones as Potential Inhibitors of Penicillin-Binding Proteins

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Dedicated to Professor Alain Krief

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Novel bicyclic 2-azetidinones, in which the β-lactam moiety is embedded in a 1,3-bridging large ring, have been studied experimentally and theoretically. The compounds were prepared from (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-4-propyl-2-azetidinone (**3**) by sequential N1 and O5 functionalization with ω-alkenyl chains by acylation and/or alkylation reactions. Cyclization by ring-closing metathesis (RCM) gave a series of 12- and 13-membered-ring compounds **7**, **12b**,**c**, **17b**,**c** and **24** featuring the internal HC=CH double bond with a preferential (*E*) configuration, and then the corresponding saturated 1,3-bridged bicycles **8**, **13b**,**c**, **18b**,**c** and **25** after hydrogenation. Bridges of 9–11 atoms were inaccessible and bridges of 12 atoms appeared favoured over those with 13 atoms according to ab initio quantum chemistry calculations. This was confirmed experimentally because ω-alkenyl double-bond migration occurred in competition with the RCM reaction in the case of 13-atom precursors, leading to a mixture of 12- and 13-membered rings. Modelling of the reactivity of our 1,3-bridged 2-azetidinones, towards hydrolysis and processing by serine enzymes, highlighted the important roles of geometrical and conformational factors and predicted a modest "acylating power" in comparison with classical penam compounds (antibiotics). Biochemical evaluation against the R39 bacterial enzyme (D,D-peptidase) revealed a weak inhibition effect of the 13-membered-ring 1,3-bridged *O*,*N*-bis(acylated) azetidinones **7** and **8**.

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Introduction

β-Lactam (i.e., 2-azetidinones) antibiotics are still the main drugs given, in the form of penicillins and cephalosporins, to treat infections caused by bacteria. These molecules disturb the final step of bacterial cell wall biosynthesis by inhibiting the D,D-transpeptidase enzymes involved in the cross-linking of peptidoglycan strands.[1] β-Lactamases are bacterial defence enzymes that very efficiently hydrolyse the β-lactam moiety in practically all classes of β-lactam antibiotics.[2] The production of these enzymes is the most common resistance mechanism of bacteria and nowadays represents a major challenge in human health.[3]

To overcome the action of the β-lactamases, the structures of the existing β-lactam drugs have to be altered. This has stimulated a lot of work devoted to novel 2-azetidinone derivatives that act as antibiotics or inhibitors of β-lactamases.[4] D,D-Transpeptidases and most of the β-lactamases are serine proteases. Their mechanism of action for processing 2-azetidinone is well established:[5] an acyl-enzyme intermediate is formed by nucleophilic attack of the Oγ atom of the active serine on the azetidinone carbonyl group followed by N–C(O) bond cleavage assisted by acidic and basic residues of the catalytic pocket involved in the proton transfer. Acyl-enzymes are stable entities in the case of the inhibition of D,D-transpeptidases. These esters can also be rapidly hydrolysed in the β-lactamases with regeneration of the active enzymes enabling the antibiotics to reach their targets.

Traditionally, the search for novel β-lactam drugs has been based on strained bicyclic 1,4-fused structures with a view to increasing the so-called "acylating power" of the twisted amide motif of the 2-azetidinone ring.[6] This could be illustrated by the recent development of carbapenem antibiotics (Figure 1), often considered as "last-resort" drugs in the treatment of infections due to resistant bacteria.[7] Another strategy involves the discovery of non-β-lactam active compounds, either by diversity-oriented synthesis[8] or by the rational design of penicillin mimics.[9]

Recently, we indicated that we would investigate a new family of bicyclic 2-azetidinones, in which the β-lactam mo-

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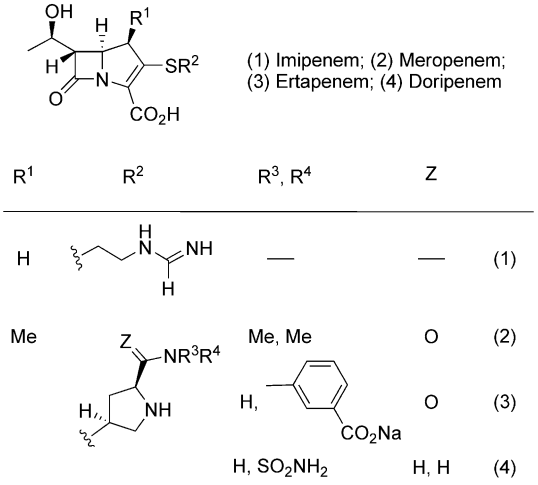

Figure 1. Chemical structures of the carbapenems in clinical use.

tif is embedded in a 1,3-bridging large ring.[10] Our idea was to decrease the activation barrier of the 2-azetidinone N–C(O) bond cleavage by increasing the conformational adaptability of the macrocyclic structure that would be involved in the reorganization of the atoms.

Our target molecules **A** are depicted in Figure 2. They are related to the carbapenem family by virtue of the C3 side-chain and the C3–C4 stereochemistry. However, the 1,4-fused cyclopentenyl ring, decorated with the bulky substituent SR^2, has been replaced by a large 1,3-bridging ring fixed on the N1 and O5 heteroatoms through alkyl and/or acyl functions. The C4 substitution of the carbapenems is simply mimicked with an *n*-propyl chain.

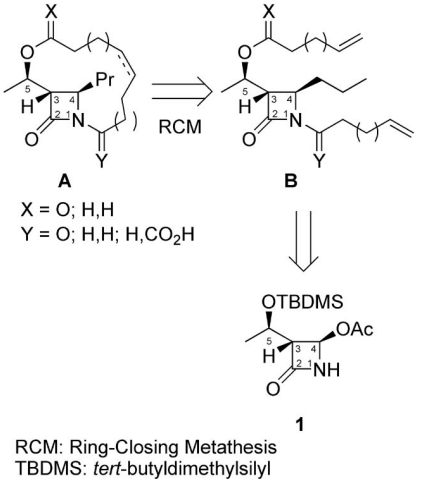

Figure 2. Bicyclic target molecules.

In this article we describe the synthesis of four families of compounds **A** and support our experimental results by ab initio quantum chemistry calculations. The reactivities of selected azetidinones versus penicillin binding proteins (PBPs) have been evaluated theoretically and in vitro against representative isolated bacterial enzymes. We can show that modest inhibitors featuring non-traditional β-lactam bicyclic cores have been developed.

Results and Discussion

Synthesis

The synthesis of 1,4-fused bicyclic β-lactams is well documented, because such structures constitute the pharmacophores of penicillin- and cephalosporin-like compounds. Novel structures that include small, medium or large fused rings are continually prepared by making use of various cyclization methods.[11] On the other hand, 1,3-bridged bicyclic β-lactams have scarcely been reported. A few strained derivatives have been obtained by carbenoid insertion reactions into the N–H lactam bond,[12] but large-ring 1,3-bridged structures require further exploration.[13]

We decided to use the ring-closing metathesis (RCM) reaction to achieve the synthesis of bridged 2-azetidinones with the general structure **A** (Figure 2). This strategy has already proven to be very efficient in the synthesis of various nitrogen-containing polycyclic systems[14] and was successfully used in our preliminary work dealing with 1,3-bridged 4-acetoxy-2-azetidinones.[10] Accordingly, the key intermediates are the monocyclic 2-azetidinones **B** equipped with two ω-alkenyl chains (Figure 2). The commercially available acetoxyazetidinone **1** is the starting material that provides the required C3 substitution and the configurations of the three chiral centres of the penem.

4-Allyl-2-azetidinone **2** was prepared according to Kang's protocol[15] and transformed into precursor **3** by catalytic hydrogenation (90% overall yield) with retention of configuration. *N*-Acylation with 4-pentenoyl chloride and pyridine was performed in dichloromethane (DCM) at reflux. Treatment of **4** with a cold mixture of acids (HCl/AcOH) in acetonitrile deprotected the silyl ether without touching the β-lactam function.[10] The alcohol **5** could be acylated as previously to furnish the cyclization precursor **6** in 86% yield after chromatography (Scheme 1). Treatment of **6** with the Grubbs catalyst (second generation)[16] under the usual conditions (5 mol-% of catalyst and substrate dilution of 5 mM) led readily to the 1,3-bridged azetidinone **7**; a high yield (95%) was obtained in DCM at room temperature, and the use of $Ti(OiPr)_4$ as additive was not required.[17] From ^1H NMR analysis of the crude product we concluded that a single stereoisomer was obtained, the HC=CH bond in the bridge having an (*E*) configuration ($^3J_{H,H}$ = 15.5 Hz, as determined by selective decoupling). Finally, catalytic hydrogenation quantitatively furnished the *N*,*O*-bis(acylated) azetidinone **8** (member of the first family of 1,3-bridged 2-azetidinones.[10]).

N-Alkylation of precursor **3** was realized under phase-transfer conditions inspired by Genêt et al.:[14c] a mixture of powdered KOH, KI, ω-alkenyl bromides, azetidinone and catalyst in dry tetrahydrofuran (THF) was stirred overnight to produce *N*-propenyl- (**9a**), *N*-butenyl- (**9b**) and *N*-pentenylazetidinones (**9c**) in good yields after chromatography

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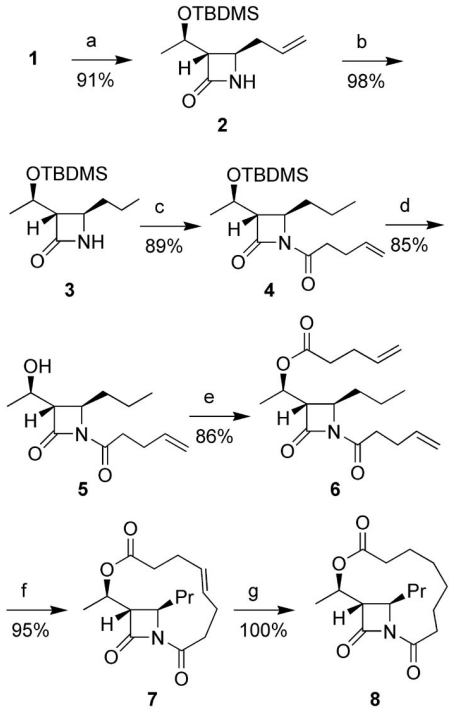
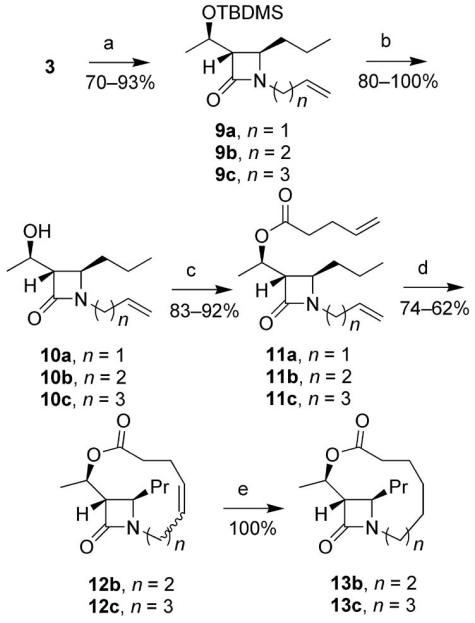


Scheme 1. Synthesis of the *N*,*O*-bis(acyl) derivatives (Family 1). Reagents and conditions: (a) In (2 equiv.), KI (3 equiv.), allyl bromide (3 equiv.), DMF, room temp.; (b) H_2, Pd/C (5 mol-%), EtOAc, room temp.; (c) 4-pentenoyl chloride, pyridine, CH_2Cl_2, reflux; (d) HCl/AcOH (5:7), CH_3CN, 0 °C; (e) 4-pentenoyl chloride, pyridine, CH_2Cl_2, room temp.; (f) 5 mol-% Grubbs cat. (2nd generation), CH_2Cl_2, room temp.; (g) H_2 (1 atm), Pd/C (5 mol-%), EtOAc, room temp.

(Scheme 2). Alcohol deprotection and acylation with 4-pentenoyl chloride, as described above, led to the key intermediates **11a**–**c**. Purified compound **11c** was submitted to the RCM conditions used for the preparation of **7** (DCM, 20 °C). The cyclized azetidinone **12c** was formed in moderate yield as a mixture of (*E*)/(*Z*) stereoisomers. In comparison with precursor **6**, in which N1 forms part of an imide function, N1 of precursor **11c**, forming part of an amide function, should be able to form a complex with the metal centre of the Grubbs catalyst and so contribute to its deactivation. Indeed, by adding Ti(O*i*Pr)$_4$ (20 mol-%) to the reaction mixture,[17] we improved the yield of **12c**. Finally, the best conditions were obtained in toluene at 80 °C, which gave 100% conversion, as determined by ^{1}H NMR analysis. The NMR spectrum showed the presence of (*E*)/(*Z*) stereoisomers of **12c** and byproducts still containing the azetidinone motif (ratio of main products/byproducts ≈ 75:25). Column chromatography allowed the recovery of pure **12c** in 62% yield [(*E*)/(*Z*) ratio = 60:40] and unidentified bicyclic azetidinones in 19% yield. Catalytic hydrogenation solved this problem: reduction of **12c** quantitatively afforded the 13-membered-ring bridged azetidinone **13c**, whereas reduction of the unknown mixture yielded the 12-membered-ring bridged azetidinone **13b**. We concluded that under our RCM conditions [5 mol-% Grubbs catalyst, 20 mol-% Ti(O*i*Pr)$_4$, 5 mM dilution of **11c**, toluene, 80 °C, 20 h], migration of the *N*-pentenyl double bond partially occurred before cyclization,[18,19] thus leading to the formal extrusion of one CH_2 motif in the bridge. Treatment of precursor **11b** under the previous RCM conditions (but with 2.5 mol-% of catalyst) gave the cyclized compound **12b** as an (*E*)/(*Z*) mixture [(*E*)/(*Z*) ratio = 70:30] in 74% yield after purification. Besides NMR spectroscopy, gas chromatography (GC) was also used to analyse the crude cyclization mixtures: RCM of **11c** gave two major products with retention times (t_r) of 37.0 (**12c**) and 35.4 min (**12b**), and RCM of **11b** led to one major product with t_r = 35.4 min (**12b**). Whatever the RCM conditions applied, we never succeeded in cyclizing the precursor **11a**: thus, the 11-membered-ring bridged azetidinones (namely **12a** and **13a**, with *n* = 1) are not accessible in this second family of target compounds (*N*-alkyl,*O*-acyl derivatives, Scheme 2).



Scheme 2. Synthesis of *N*-alkyl,*O*-acyl derivatives (Family 2). Reagents and conditions: (a) KOH (1.5 equiv.), KI (2 equiv.), Bu_4NHSO_4 (0.04 equiv.), alkenyl bromide (3 equiv.), THF, room temp.; (b) HCl/AcOH (5:7), CH_3CN, 0 °C; (c) 4-pentenoyl chloride, pyridine, CH_2Cl_2, room temp.; (d) 2.5–5 mol-% Grubbs cat. (2nd generation), Ti(O*i*Pr)$_4$ (20 mol-%), toluene, 80 °C; (e) H_2 (1 atm), Pd/C (5 mol-%), EtOAc, room temp.

Starting from alcohol **10**, we performed etherification reactions under the usual Williamson's conditions (Scheme 3). The alcohol was deprotonated with NaH in dimethylformamide at 0 °C and then treated with 2-propenyl, 3-butenyl or 4-pentenyl bromide (3 equiv.) in the presence of KI except for the synthesis of **16b** (20 °C, 6–8 h). Yields of purified (column chromatography) azetidinones **14**, **15** and **16** were moderate to good when the C5 chains were the 2-propenyloxy (*m* = 1) and 4-pentenyloxy (*m* = 3) groups. Products bearing the 3-butenyloxy (*m* = 2) chain at C5 were never obtained: elimination reaction occurred with 3-butenyl bromide instead of nucleophilic substitution. The

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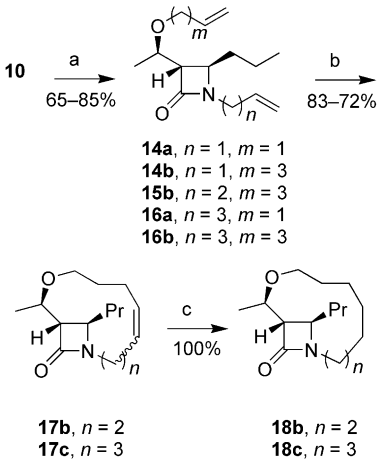
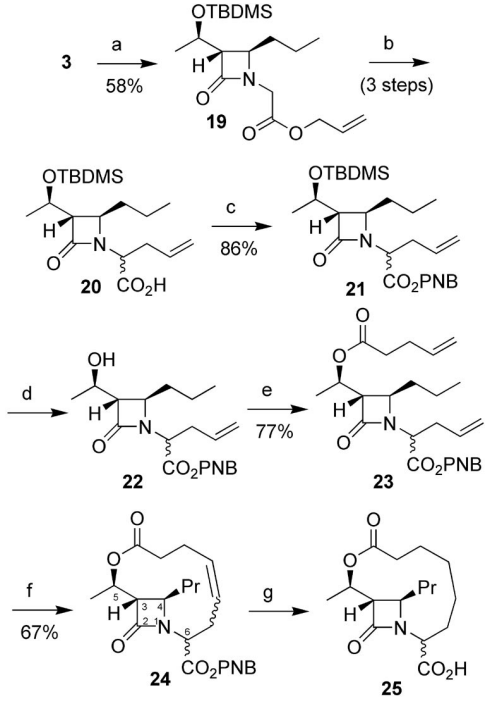
cyclization of the key intermediates **14**–**16** could be realized only with the 4-pentenyloxy (m = 3) precursors **15b** and **16b**, leading to the 12- and 13-membered-ring bridged azetidinones **17b** and **17c** in 83 and 72% yields, respectively, after purification by column chromatography. Here again, Ti(O*i*Pr)$_4$ was required as additive to the Grubbs catalyst to complete the RCM reaction. Compounds **17b** and **17c** were obtained as (*E*)/(*Z*) mixtures of stereoisomers [(*E*)/(*Z*) ratio = 73:27 and 25:75, respectively, by ^{1}H NMR analysis], and **17c** was accompanied by the formation of **17b** as the byproduct[18,19] (8% isolated yield after chromatography). The formation of the (*Z*) configuration of the HC=CH double bond in the major stereoisomer of **17c** was assigned on the basis of the $^3J_{H,H}$ coupling constant of 10.9 Hz (determined by selective decoupling). As above, **17b** was identified as a side-product of **17c** by NMR analysis of the separated compounds (comparison with an authentic sample after hydrogenation) and by GC analysis of RCM crude mixtures. Starting from **16b**, we observed two products with t_r = 33.5 (**17c**) and 31.2 min (**17b**), whereas **15b** gave one product with t_r = 31.2 min (**17b**). Finally, catalytic hydrogenation led to the *N*,*O*-bis(alkylated) compounds **18b** and **18c** (members of the third family of 1,3-bridged 2-azetidinones, Scheme 3). As previously (see **11a**), the 11-membered-ring compounds were not accessible from **14b** (n = 1, m = 3) or **16a** (n = 3, m = 1), nor the nine-membered-ring compound from **14a** (n = m = 1). The failure of the RCM process in these cases may result not only from conformational and steric drawbacks, but also from the rapid isomerization of the *N*/*O*-allyl chains catalysed by Ru complexes, leading finally to an *N*/*O*-deprotection-like reaction.[20]



Scheme 3. Synthesis of *N*,*O*-bis(alkyl) derivatives (Family 3). Reagents and conditions: (a) NaH (1.1 equiv.), alkenyl bromide (3 equiv.), KI (3 equiv.), DMF, 0 °C to room temp.; (b) 2.5–5 mol-% Grubbs cat. (2nd generation), Ti(O*i*Pr)$_4$ (20 mol-%), toluene, 80 °C; (c) H_2 (1 atm), Pd/C (5 mol-%), EtOAc, room temp.

Functionalization of the N1-alkenyl chain with a carboxy group (penem mimic) was successfully achieved by using the strategy of Barrett and co-workers.[21] Azetidinone **3** was first *N*-alkylated with allyl bromoacetate (NaH, DMF, 0 °C). The resulting ester **19** (Scheme 4) was treated at low temperatures in THF with lithium hexamethyldisilazide (LiHMDS) and trimethylsilyl chloride (TMSCl) to produce an *O*-silyl enolate intermediate that suffers a Claisen–Ireland sigmatropic rearrangement when the temperature was increased from –78 to 80 °C (Scheme 5). In situ hydrolysis of the silyl ester intermediate by methanol gave the acid **20** as a 66:33 mixture of diastereoisomers. This crude product was directly converted into the *p*-nitrobenzyl (PNB) ester **21** under solid/liquid phase-transfer conditions. Chromatographic purification afforded **21** in 86% yield from **19**. Subsequently *O*-deprotection, *O*-acylation with 4-pentenoyl chloride and cyclization by RCM [2.5 mol-% catalyst, 20 mol-% Ti(O*i*Pr)$_4$, toluene, 20 °C, 24 h] were performed; this last reaction was carried out at room temperature to avoid degradation of the PNB ester. After chromatography, **24** was isolated in 67% yield as a mixture of diastereoisomers at C6 (ratio of 66:33) and (*E*)/(*Z*) stereoisomers of the HC=CH double bond [(*E*)/(*Z*) ratio = 75:25]. Finally, catalytic hydrogenation was performed to reduce the double bond and simultaneously deprotect the carboxy function to furnish the 12-membered-ring bridged azetidinone **25** belonging to the fourth family (penem-like structures, Scheme 4). Unfortunately, this compound could not be purified by chromatography.



Scheme 4. Synthesis of penem-like large-ring derivatives (Family 4). Reagents and conditions: (a) NaH (1.2 equiv.), allyl bromoacetate (2 equiv.), DMF, 0 °C to room temp.; (b) see Scheme 5; (c) K_2CO_3 (1.5 equiv.), Bu_4NHSO_4 (0.1 equiv.), *p*-nitrobenzyl bromide (2 equiv.), DMF, room temp.; (d) HCl/AcOH (5:7), CH_3CN, 0 °C; (e) 4-pentenoyl chloride, pyridine, CH_2Cl_2, room temp.; (f) 2.5–5 mol-% Grubbs cat. (2nd generation), Ti(O*i*Pr)$_4$ (20 mol-%), toluene, room temp.; (g) H_2 (1 atm), Pd/C (5 mol-%), EtOAc, room temp.

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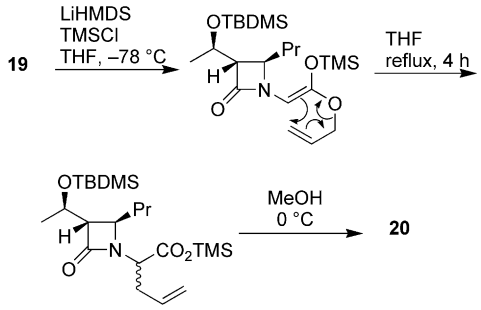

Scheme 5. Sigmatropic rearrangement.

Theoretical Study[22]

A number of stable conformers were found for the monocyclic precursors **6**, **11**, **15**, **16** and the corresponding bridged bicyclic products **7**, **12** and **17**. This was examined by ab initio quantum chemistry calculations in vacuo at the B3LYP level of theory with the double basis set 6-31G(d). For at least two conformers of the starting azetidinones, the related conformers of the bicyclic azetidinones were computed with the HC=CH double bond in the (*E*) or (*Z*) configuration. Two representative conformers **I** and **II** of precursor **11c** are shown in Figure 3. The relative energy differences between conformers **I** and **II** of the RCM products are collected in Table 1 and were calculated with respect to the more stable conformer **II**. After cyclization, conformer **II** of the *O*,*N*-bis(acylated) product **7** is more stable for the (*E*) stereoisomer, whereas conformers **II** of the series **12** (*O*-acyl,*N*-alkyl) and **17** [*O*,*N*-bis(alkyl)] are almost equally stabilized for both stereoisomers. This is consistent with our experimental data: **7** was recovered as a single (*E*) stereoisomer and **12b**,**c** and **17b**,**c** were mixtures of (*E*)/(*Z*) stereoisomers, with the (*Z*) isomer being the major compound for **17c** only.

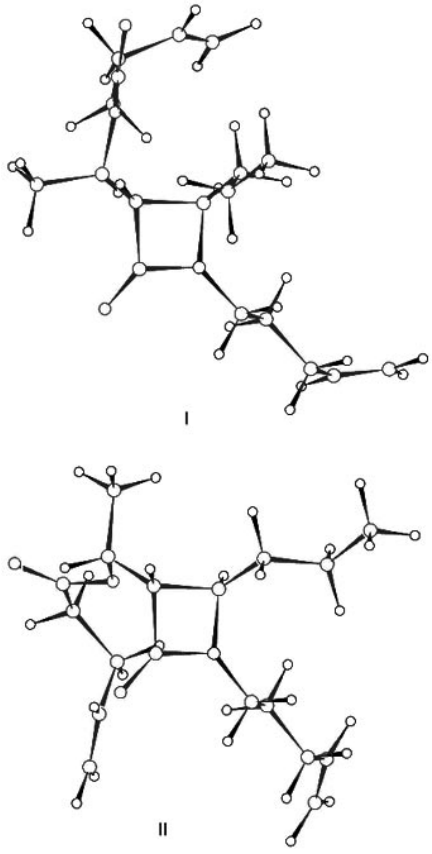

Figure 3. Two representative conformers of **11c**. Conformer **II** is more stable than **I**.

Table 1. Energy differences between conformers **I** and **II**, given as a function of the HC=CH double bond configuration.

Compound	Energy [kcal mol^{-1}]	
	(*E*) isomer	(*Z*) isomer
7	5.30	9.19
12b	11.99	12.00
12c	9.48	9.19
17b	9.73	11.68
17c	4.48	3.64

The heats of formation of the bicyclic compounds by RCM reaction were calculated by reference to the open precursors minus ethylene (Table 2). All reactions are slightly endothermic. The (*E*) isomer has, in general, a smaller heat of formation than the (*Z*) isomer. Moreover, the heat of formation of the (*E*) or (*Z*) conformer **I** is higher than that of the more stable conformer **II**. Finally, when comparing the esters **12b** and **12c** and the ethers **17b** and **17c**, the formation of the 12-membered rings **12b** and **17b** appears to be easier than the closure of the 13-membered rings **12c** and **17c**. Experimentally, we found that the cyclization of **11c** was quite sluggish and led to both 13- and 12-membered rings by double-bond migration in the open precursor. A similar trend was observed during the RCM cyclization of **16b**. The co-existence of conformers could be proved experimentally in one case. Fortunately, after HC=CH double-bond hydrogenation, the 12-membered-ring 1,3-bridged azetidinone **12b** [mixture of (*E*)/(*Z*) isomers] gave a single compound **13b**, which crystallizes slowly in an acetone/diethyl ether mixture (1:2, v/v). X-ray diffraction analysis of a single crystal revealed two conformers in the same unit cell: they differ by the orientation of the *n*-propyl chain and the spatial arrangement of the bridging cycle, as shown in Figure 4.[23]

Table 2. Heats of formation [kcal mol^{-1}] for conformers **II** and **I**, given as a function of the HC=CH double-bond configuration.

Compound	(*E*) isomer		(*Z*) isomer	
	Δ*E* (**II**)	Δ*E* (**I**)	Δ*E* (**II**)	Δ*E* (**I**)
7	4.91	9.02	12.05	12.28
12b	3.51	8.94	4.93	10.35
12c	6.00	8.39	7.80	10.77
17b	4.80	14.25	4.79	12.28
17c	6.58	8.18	7.01	9.46

Two reactivity models were considered to mimic the processing of monocyclic and bridged bicyclic azetidinones by serine enzymes. Both are concerted mechanisms involving

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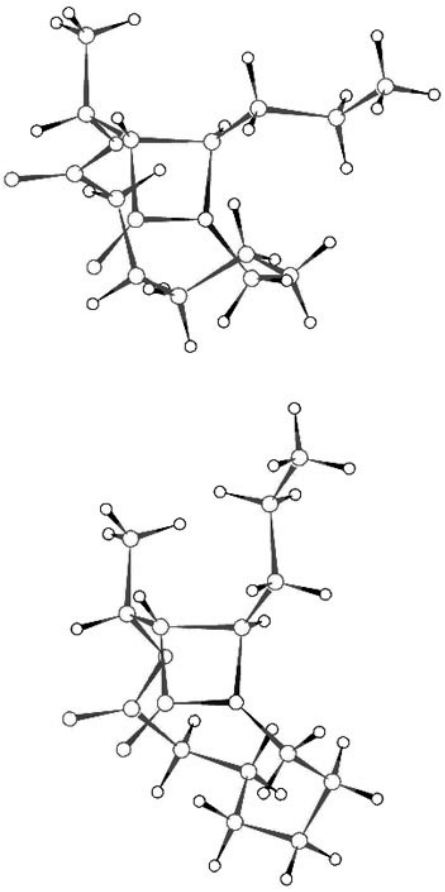

Figure 4. X-ray structure of **13b** showing two conformers in the unit cell.

nucleophilic attack on the β-lactam carbonyl group accompanied by N–C(O) bond cleavage and proton shuttle, as described previously.[10] Briefly, Model A considers the duplex H_2O/H_2O as a nucleophile, whereas Model B considers the triplex 2-(formylamino)-1-ethanol/H_2O/imidazole as a mimic of the active site catalytic triad of the trypsin enzyme family. For Model A, both approaches to the azetidinone ring can be considered, that is, from either the α or β face of the small cycle,[24] whereas for Model B, only the attack from the α face is the relevant one.[10] Owing to the size of the analysed systems, the activation energies (E_A) have been computed at the RHF level with the minimal

Table 3. Activation energies E_A for concerted nucleophilic attack on azetidinones. Calculations for conformers **I**.

Entry	Compound	E_A [kcal mol^{-1}]			
		Model A (β face)	Model A (α face)	Model B (α face)	Family/bridge size
1	**6**	29.54	38.34	27.16	
2	(*E*)-**7**	23.13	36.61	25.40	1/13
3	**8**	20.24	34.98	30.63	1/13
4	**11b**			25.87	
5	(*E*)-**12b**			30.25	2/12
6	(*Z*)-**12b**			30.43	2/12
7	**11c**			26.08	
8	(*E*)-**12c**	29.08	36.58	25.88	2/13
9	(*Z*)-**12c**			26.66	2/13
10	**15b**			26.80	
11	(*E*)-**17b**			32.53	3/12
12	(*Z*)-**17b**			34.26	3/12
13	**16b**			27.15	
14	(*E*)-**17c**	32.49	43.21	30.32	3/13
15	(*Z*)-**17c**			35.19	3/13
16	penam		26.56	14.62	reference

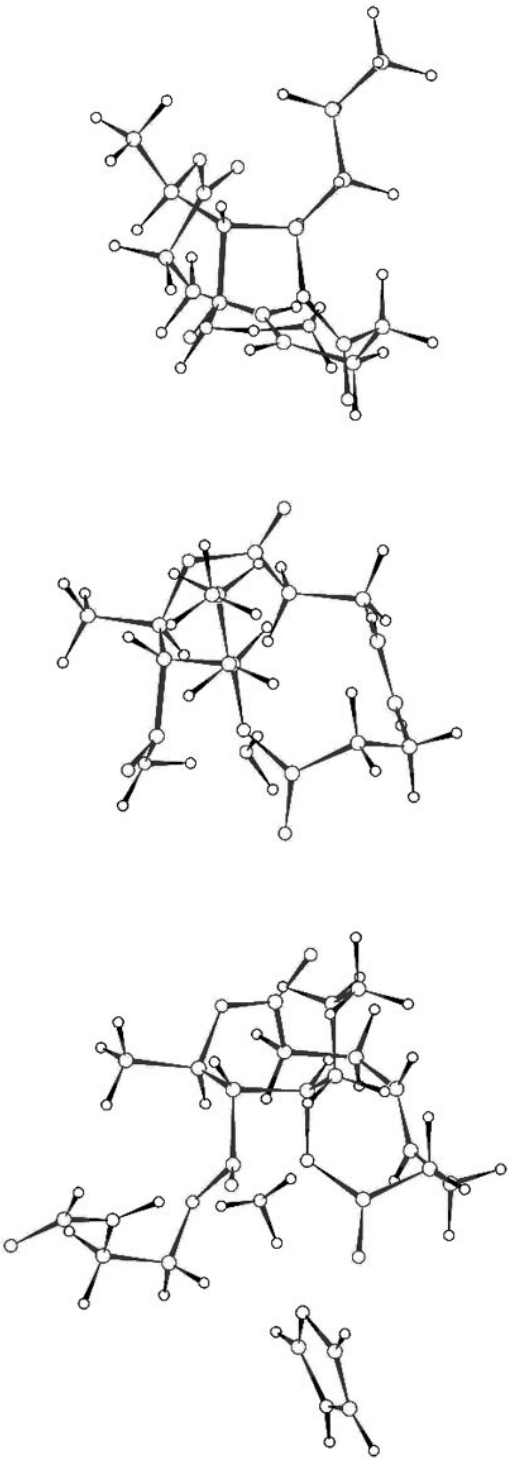

Figure 5. Structures of the transition states of azetidinone **7** processed by using Model A (attack on the α and β face) and Model B (attack on the α face).

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basis set MINI-1′. The results are collected in Table 3.[25] The chemical hydrolysis model (Model A) clearly shows that nucleophilic attack by water on the β face is favoured over the α face. Indeed, this corresponds to HO–C(O) bond formation from the less hindered face, because the large bridging ring unfolds over the azetidinone α face in all compounds. The *O*,*N*-bis(acylated) bicyclic compounds **7** and **8** (Entries 2 and 3) appeared to be more reactive than the *O*-acyl,*N*-alkyl and *O*,*N*-bis(alkyl) derivatives **12c** and **17c** (Entries 8 and 14) featuring the same bridge size (13-membered ring). Also, the bicyclic compounds were predicted to be more reactive than the monocyclic precursor (compare **7** and **8** to **6**). Computation of Model B revealed a different behaviour. On the basis of nucleophilic attack on the α face, as should occur in the serine enzyme active site, the monocyclic precursors **11b**, **15b** and **16b** (Entries 4, 10 and 13) were found to be more reactive than the corresponding bicyclic azetidinones **12b**, **17b** and **17c** (Entries 5, 6, 11, 12 and 14, 15), and in the bicyclic series, the (*E*) isomers were favoured over the (*Z*) isomers. Bicycle **7** (Entry 2) was predicted to be more reactive than its precursor **6** (Entry 1), but less reactive after reduction of the HC=CH bond giving compound **8** (Entry 3). Very similar reactivities were calculated for **11c** (open precursor, Entry 7) and the corresponding (*E*) and (*Z*) isomers of **12c** (Entries 8 and 9). Interestingly, the E_A values of all the monocyclic azetidinones, **6**, **11b**, **11c**, **15b** and **16b**, are in the range between 25.9 and 27.1 kcal mol^{-1}, showing no particular influence of the *O*,*N*-acyl motifs and/or chain lengths on reactivity. For the bicyclic azetidinones, the E_A values covered a larger range, from 25.4 to 35.2 kcal mol^{-1}; no correlation with the bridge size (12- or 13-membered ring) could be found. The ease of atom reorganization during the azetidinone N–C(O) bond cleavage depends mainly on torsion (or eclipse) strains and transannular interactions, hardly predictable when sp^2 carbon atoms of the bridge are replaced with sp^3 ones (C=O replaced with CH_2; CH=CH reduced to CH_2–CH_2). Figure 5 shows the structures of the transition states (TS) of the 1,3-bridged azetidinone (*E*)-**7** processed by Models A and B.

Biochemical Evaluation[26]

The β-lactams **6**–**8** were evaluated for their potential inhibition effect on bacterial serine enzymes. Both theoretical Models A and B predicted that the 13-membered-ring bridged compound (*E*)-**7** should be our best acylating reagent, but quite modest in relation to the penam reference (Table 3, Entry 16).

The activities of compounds **6**–**8** against the β-lactamase TEM-1 from *E. coli* (Class A enzyme)[27] was assayed in a competition experiment with a chromogenic substrate (nitrocefine); none of the compounds was found to be active at a concentration of 100 μM. R39 from *Actinomadura* is a low-molecular-weight D,D-carboxypeptidase-transpeptidase enzyme usually used for a preliminary screening of penicillin-like compounds.[28] R39 and the tested azetidinones (100 μM) were incubated (16 h, 30 °C), and then fluorescent ampicillin (25 μM) was added. After 45 min, the peptidase was denatured and the fluorescence intensity measured. Thus, in this protocol, the azetidinones **6**–**8** are supposed to be capable of acylating R39 (giving stable acyl-enzyme intermediates), and the residual activity of R39 is determined by the amount of covalent R39–ampicillin complexes formed, as measured by fluorescence spectroscopy. The results are presented in Table 4 as percentages of the R39 initial activity, low values indicating active compounds. In such a test, the limiting value for a "hit" is 80%. Interestingly, the large-ring 1,3-bridged β-lactams **7** and **8** were found to be active R39 inhibitors, whereas the monocyclic precursor **6** was inactive. We similarly evaluated **6**–**8** against a set of high-molecular-weight D,D-peptidases responsible for bacterial resistance to β-lactam antibiotics,[29] namely PBP2a from *S. aureus*, PBP5fm from *E. faecium* and PBP2x from *S. pneumoniae*. β-Lactam **7** was weakly active compared with PBP2a, whereas **8** was modestly active compared with PBP2x (Table 4). As a control experiment, the activities of β-lactams **6**–**8** against a mammalian serine enzyme, PPE (Porcin Pancreatic Elastase), were assayed in a competition experiment with a chromogenic substrate (*N*-succinyl-L-alanyl-L-alanyl-L-alanyl-*p*-nitroanilide);[30] all of the compounds were inactive at a concentration of 100 μM.

Table 4. Inhibition of PBPs.[a]

Compound	R39 (0.8 μM)	PBP2a (2.5 μM)	PBP5fm (2.5 μM)	PBP2x (0.8 μM)
6	110 ± 11	107 ± 14	107 ± 2	101 ± 3
7 (*E*)	80 ± 10	92 ± 5	100 ± 11	103 ± 5
8	77 ± 12	95 ± 7	98 ± 4	91 ± 6
Penicillin G	n.d.	13 ± 3	10 ± 3	< 5

[a] Results are expressed as percentages of the initial activity. Means of at least three independent experiments.

Conclusions

RCM is a well-established strategy for achieving small-, medium- or large-ring bicyclic systems. We have documented a novel application of RCM for achieving bridged azetidinones designed as potential inhibitors of PBPs. The scope and limitations of the cyclization of precursors **B** into target molecules **A** (Figure 2), depending on the nature of the X and Y functions and the ring size, were determined. Bridges of 9–11 atoms are inaccessible for at least two reasons other than simply angular strain: (i) *O*-alkylation with 3-butenyl bromide (*m* = 2) failed and (ii) cleavage of the *O*,*N*-allyl motifs occurred under RCM conditions (*n* = 1; *m* = 1). The accessibility of 13-membered bridges depends on the azetidinone *N*-functionalization: the *N*-acyl derivative **6** reacted rapidly and quantitatively (DCM, 20 °C), whereas the *N*-alkyl derivatives **11c** and **16b** required the presence of $Ti(OiPr)_4$ as an additive to avoid deactivation of the ruthenium intermediate species; the cyclization process required thermal activation (toluene, 80 °C) and competition with double-bond migration occurred. For electronic and con-

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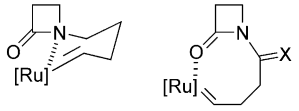
formational reasons, illustrated in Figure 6, Ru–azetidinone complexes should be formed more easily in the case of *N*-alkyl derivatives (a) than with *N*-acyl (b) derivatives. Twelve-membered bridges formed readily from precursors **11c**, **15b** and **23** under modified RCM conditions (Ru catalyst + Lewis acid). GC analysis showed that the cyclized products **12b** and **17b** are identical to the side-products recovered during the synthesis of 13-membered bridged compounds. Accordingly, olefin migration occurs mainly in the *N*-alkenyl rather than in the *O*-alkenyl chain.



(a) (b) X = O; H,H

Figure 6. Possible ways of sequestrating Ru intermediates.

Our theoretical studies supported well the experimental data of the compounds synthesized (ring size and HC=CH stereochemistry). Modelling of the reactivity of the 1,3-bridged azetidinones in the active site of the serine enzymes illustrated the important role of geometrical factors (attack of the α or β face), probably as crucial as the conformational factors. Despite the great complexity of our systems, we could predict that large-ring 1,3-bridged 2-azetidinones should be endowed with acceptable "acylating power" (E_A values of around 30 kcal mol^{-1}). Fortunately, the preliminary biochemical evaluations confirmed the bicyclic compounds **7** and **8** as modest inhibitors of the R39 enzyme and very weak inhibitors of two resistant PBPs, whereas the open precursor **6** was not active at all. These results remain, however, questionable because a related series of compounds previously reported,[10] featuring an acyloxy chain (OAc) at C4 instead of the *n*Pr chain, showed contrasting behaviour: the open precursor was a good inhibitor of R39 and the cyclized derivatives (unsaturated and saturated) were inactive towards the same enzyme, but all members of this C4–OAc series weakly inhibited PBP2a.

Definitively, the search for PBP inhibitors remains a challenging task. Nevertheless, we have prepared non-traditional bicyclic β-lactams and in doing so developed novel biochemically active compounds showing that high angular strain (cf. penems) is not the only valuable strategy that can be applied to reach our goal.

Experimental Section

General: Manipulations were performed under argon in flame-dried glassware. Reagents were used as received, and anhydrous solvents (CH_2Cl_2, DMF, THF and toluene) were purchased from commercial suppliers. TLC analyses were performed on aluminium plates coated with silica gel $60F_{254}$ (Merck) and visualized with a $KMnO_4$ solution and UV (254 nm) detection. Melting points were measured with an Electrothermal apparatus calibrated with benzoic acid (melting points are uncorrected). Column chromatography was performed on silica gel Merck 60 (40–60 μm). GC analyses were performed with a CE Instruments GC-8000 Top with an MN OPTIMAS capillary column (30 m × 0.25 mm; 0.25 μm) by using a temperature program of 5 °C/min from 50 to 290 °C. NMR spectra were recorded with a Varian Gemini 200 spectrometer at 200 (^{1}H) and 50 MHz (^{13}C) or with a Bruker Avance 500 spectrometer at 500 (^{1}H) and 125 MHz (^{13}C) in $CDCl_3$ with TMS as the internal standard. IR spectra were recorded with a Shimadzu FTIR-8400S spectrometer; compounds were deposited on NaCl plates as a thin film by evaporation of CH_2Cl_2 from solution. High-resolution mass spectra were recorded at the Mass Spectrometry Service of the University of Mons-Hainaut, Belgium.

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-(prop-2-enyl)-2-azetidinone (2):[15] KI (1.733 g, 10.44 mmol, 3 equiv.) and allyl bromide (0.90 mL, 10.44 mmol, 3 equiv.) were added to a stirred suspension of indium powder (800 mg, 6.96 mmol, 2 equiv.) in dry DMF at room temp. The mixture was stirred under argon for 1 h before the addition of acetoxyazetidinone **1** (1 g, 3.48 mmol). After 4 h, the solution was diluted with diethyl ether (50 mL), washed with a saturated NH_4Cl solution (50 mL) and brine (2 × 50 mL), dried with $MgSO_4$, and the solvent was removed under reduced pressure to provide a white solid (930 mg). Purification by flash chromatography (CyHex/AcOEt, 5:2) furnished pure compound **2** (850 mg, 91%). TLC (CyHex/AcOEt, 5:3): R_f = 0.54. M.p. 81.5–82.6 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 6.80 (br. s, 1 H, NH), 5.74–5.86 (ddt, 1 H), 5.09–5.14 (m, 4 H), 4.17 (qt, 1 H), 3.68 (dt, 2 H), 2.77 (dd, 2 H), 2.3–2.5 (m, 2 H), 1.20 (d, 2 H), 0.86 (s, 9 H), 0.05–0.06 (2 s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 169.1, 133.4, 117.8, 65.4, 63.5, 50.4, 39.2, 25.6, 22.6, 17.8, –3.0, –3.7 ppm.

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-propyl-2-azetidinone (3): Precursor **2** (1.33 g, 4.94 mmol) dissolved in AcOEt (15 mL) was placed under H_2 (1 atm) at room temp. in the presence of Pd catalyst (26 mg, 0.25 mmol, 0.05 equiv.) for 5 h. Then Pd/C was removed by filtration and the solution concentrated under vacuum to provide pure product **3** as a white solid (1.31 g, 98%). TLC (CyHex/AcOEt, 5:3): R_f = 0.59. M.p. 73 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 6.16 (br. s, 1 H, NH), 4.14 (qd, $J_{H,H}$ = 6.2, $J_{H,H}$ = 5.1 Hz, 1 H), 3.61 (dt, $J_{H,H}$ = 1.9, $J_{H,H}$ = 6.6 Hz, 1 H), 2.69 (dd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 5.1 Hz, 1 H), 1.56 (m, 2 H), 1.35 (m, 2 H), 1.19 (d, $J_{H,H}$ = 6.2 Hz, 3 H), 0.94 (t, $J_{H,H}$ = 7.2 Hz, 3 H), 0.95 (s, 9 H), 0.0 (2 s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 169.2, 65.7, 64.3, 51.2, 37.2, 25.7, 22.6, 19.8, 17.9, 13.9, –4.4, –5.0 ppm. HRMS (TOF MS ES$^+$): calcd. for $C_{14}H_{29}NO_2Si$ 272.2046 [M + H]$^+$; found 272.2036.

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-(pent-4-enoyl)-4-propyl-2-azetidinone (4): Pyridine (0.36 mL, 4.42 mmol, 2 equiv.) and 4-pentenoyl chloride (0.48 mL, 4.42 mmol, 2 equiv.) were added to a stirred solution of β-lactam **3** (600 mg, 2.21 mmol) in dry CH_2Cl_2 (15 mL). The solution was warmed to 35 °C under argon for 24 h. Then the reaction medium was diluted with CH_2Cl_2 (50 mL) and sequentially washed with a 3.3 M HCl solution (50 mL), a saturated $NaHCO_3$ solution (50 mL), and brine (50 mL). After drying with $MgSO_4$ and concentration under vacuum, the residue was purified by flash chromatography (CyHex/AcOEt, 5:1) to provide **4** as a colourless oil (780 mg, 89%). TLC (CyHex/AcOEt, 5:1): R_f = 0.79. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.81 (ddt, $J_{H,H}$ = 6.6, $J_{H,H}$ = 10.2, $J_{H,H}$ = 16.9 Hz, 1 H), 5.06 (dd, $J_{H,H}$ = 1.6, $J_{H,H}$ = 17.1 Hz, 1 H), 4.98 (dd, $J_{H,H}$ = 1.6, $J_{H,H}$ = 10.2 Hz, 1 H), 4.24 (qd, $J_{H,H}$ = 3.4, $J_{H,H}$ = 6.0 Hz, 1 H), 4.10 (ddd, $J_{H,H}$ = 3.4, $J_{H,H}$ = 3.4, J = 8.9 Hz, 1 H), 2.79 (m, 1 H), 2.78 (dd, $J_{H,H}$ = 3.4, $J_{H,H}$ = 3.4 Hz, 1 H), 2.72 (m, 1 H), 2.38 (m, 2 H), 2.11 (m, 1 H), 1.49 (m, 1 H), 1.34 (m, 2 H), 1.20 (d, $J_{H,H}$ = 6.0 Hz, 3 H), 0.96 (t, $J_{H,H}$ = 7.2 Hz, 3 H), 0.82 (s, 9 H), 0.02 (s,

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3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 170.4, 166.7, 136.6, 115.5, 64.8, 62.3, 52.6, 35.8, 34.3, 27.9, 25.5, 22.3, 18.8, 17.7, 14.0, –4.4, –5.3 ppm. HRMS (TOF MS ES$^+$): calcd. for $C_{19}H_{35}NO_3Si$ 376.2284 [M + Na]$^+$; found 376.2296. IR (NaCl): $\tilde{\nu}_{max}$ = 1786, 1702, 1638, 1310 cm^{-1}.

(3*S*,4*R*)-3-[(1*R*)-1-Hydroxyethyl]-1-(pent-4-enoyl)-4-propyl-2-azetidinone (5): β-Lactam **4** (1.22 g, 3.46 mmol) was dissolved in CH_3CN (100 mL) with AcOH (17 M, 1.42 mL, 24.2 mmol, 7 equiv.) and HCl (12 M, 1.44 mL, 17.3 mmol, 5 equiv.) at 0 °C and stirred for 3 h. The solvent was removed and the residue diluted with AcOEt (50 mL). Then the organic phase was washed with a 10% Na_2CO_3 solution and brine (2 × 50 mL), dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (CyHex/AcOEt, 5:2) to yield **5** as a white paste (700 mg, 85%); **5** can also be used without purification in the next step. TLC (CyHex/AcOEt, 5:2): R_f = 0.45. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.71 (ddt, $J_{H,H}$ = 6.4, $J_{H,H}$ = 10.3, $J_{H,H}$ = 16.6 Hz, 1 H), 4.96 (dd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 17.1 Hz, 1 H), 4.89 (dd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 10.3 Hz, 1 H), 4.06 (qd, $J_{H,H}$ = 5.9, J = 6.4 Hz, 1 H), 3.96 (m, 1 H), 3.32 (br. s, 1 H), 2.76 (dd, $J_{H,H}$ = 2.9, $J_{H,H}$ = 5.4 Hz, 1 H), 2.68 (t, $J_{H,H}$ = 7.3 Hz, 2 H), 2.27 (td, $J_{H,H}$ = 6.8, $J_{H,H}$ = 7.3 Hz, 2 H), 2.01 (m, 1 H), 1.40 (m, 1 H), 1.27 (m, 2 H), 1.18 (d, $J_{H,H}$ = 6.4 Hz, 3 H), 0.86 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 170.6, 166.5, 136.1, 115.3, 64.2, 61.6, 53.2, 35.6, 33.9, 27.7, 21.4, 18.3, 13.7 ppm. HRMS (TOF MS ES$^+$): calcd. for $C_{13}H_{21}NO_3$ 240.1600 [M + H]$^+$; found 240.1592. IR (NaCl): $\tilde{\nu}$ = 3470, 1784, 1701, 1641, 1321 cm^{-1}.

(3*S*,4*R*)-1-(Pent-4-enoyl)-3-[(1*R*)-1-(pent-4-enoyloxy)ethyl]-4-propyl-2-azetidinone (6): Pyridine (0.17 mL, 2.10 mmol, 2 equiv.) and 4-pentenoyl chloride (0.23 mL, 2.10 mmol, 2 equiv.) were added to a stirred solution of β-lactam **5** (250 mg, 1.05 mmol) in dry CH_2Cl_2 (5 mL). The reaction was performed at room temp. under argon for 3 h. Then the reaction medium was diluted with CH_2Cl_2 (15 mL) and sequentially washed with a 3.3 M HCl solution (15 mL), a saturated $NaHCO_3$ solution (15 mL), and brine (15 mL). The organic layer was dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (CyHex/AcOEt, 10:1) to provide **6** as a pale-yellow oil (291 mg, 86%). TLC (CyHex/AcOEt, 5:1): R_f = 0.52. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.81 (ddt, $J_{H,H}$ = 6.5, $J_{H,H}$ = 10.2, $J_{H,H}$ = 16.8 Hz, 1 H), 5.77 (ddt, $J_{H,H}$ = 5.9, $J_{H,H}$ = 10.7, $J_{H,H}$ = 16.8 Hz, 1 H), 5.21 (qd, $J_{H,H}$ = 6.4, $J_{H,H}$ = 6.6 Hz, 1 H), 5.05 (dd, $J_{H,H}$ = 1.6, $J_{H,H}$ = 10.2 Hz, 1 H), 5.03 (m, 1 H), 4.99 (m, 2 H), 3.92 (m, 1 H), 2.95 (dd, $J_{H,H}$ = 3.2, $J_{H,H}$ = 6.7 Hz, 1 H), 2.78 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 2.38 (m, 2 H), 2.34 (m, 4 H), 2.15 (m, 1 H), 1.46 (m, 1 H), 1.34 (m, 2 H), 1.34 (d, $J_{H,H}$ = 6.7 Hz, 3 H), 0.95 (t, $J_{H,H}$ = 7.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 171.7, 170.5, 164.5, 136.3, 136.1, 115.6, 67.4, 59.5, 54.5, 35.9, 34.2, 33.4, 28.6, 27.8, 18.44, 18.41, 13.8 ppm. HRMS (TOF MS ES$^+$): calcd. for $C_{18}H_{27}NO_4$ 344.1838 [M + Na]$^+$; found 344.1847. IR (NaCl): $\tilde{\nu}_{max}$ = 1786, 1739, 1704, 1321 cm^{-1}.

(5*E*,11*R*,12*S*,14*R*)-11-Methyl-2,9,13-trioxo-14-pRopyl-10-oxa-1-azabicyclo[10.1.1]tetradec-5-ene (7). Method A: Grubbs catalyst (39.7 mg, 0.047 mmol, 0.05 equiv.) was added to a stirred solution of β-lactam **6** (300 mg, 0.934 mmol) in dry CH_2Cl_2 (200 mL, 5 mM). The reaction was performed at room temp. under argon for 5 h. Then the solvent was removed and the crude product purified by flash chromatography (CyHex/AcOEt, 5:2) to provide **7** as a white solid (260 mg, 95%). TLC (CyHex/AcOEt, 5:2): R_f = 0.56. M.p. 57.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.55 (qd, $J_{H,H}$ = 1.9, $J_{H,H}$ = 6.5 Hz, 1 H), 5.40 (m, $J_{H,H}$ = 15.5 Hz, 1 H), 5.33 (m, $J_{H,H}$ = 15.5 Hz, 1 H), 4.06 (ddd, $J_{H,H}$ = 3.0, $J_{H,H}$ = 3.6, $J_{H,H}$ = 9.1 Hz, 1 H), 3.27 (m, 1 H), 2.85 (dd, $J_{H,H}$ = 1.9, $J_{H,H}$ = 3.0 Hz, 1 H), 2.32 (m, 2 H), 2.25–2.39 (m, 3 H), 2.23 (m, 2 H), 2.11 (m, 1 H), 1.45 (m, 1 H), 1.31 (m, 2 H), 1.21 (d, $J_{H,H}$ = 6.6 Hz, 3 H), 0.94 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 171.6, 171.4, 165.2, 129.8, 128.3, 65.0, 59.7, 52.1, 34.7, 34.3, 33.6, 30.2, 27.9, 18.8, 18.7, 13.8 ppm. HRMS (TOF MS ES$^+$): calcd. for $C_{16}H_{23}NO_4$ 316.1525 [M + Na]$^+$; found 316.1531. IR (NaCl): $\tilde{\nu}_{max}$ = 2874–2959), 1792, 1736, 1697 cm^{-1}.

(11*R*,12*S*,14*R*)-11-Methyl-2,9,13-trioxo-14-propyl-10-oxa-1-azabicyclo[10.1.1]tetradecane (8): β-Lactam **8** was obtained from precursor **7** (260 mg, 0.91 mmol) by the procedure used for the synthesis of **3**. Filtration and concentration under vacuum furnished the reduced compound as a white solid (268 mg, 100%). TLC (CyHex/AcOEt, 5:2): R_f = 0.52. M.p. 67 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.52 (qd, $J_{H,H}$ = 2.2, $J_{H,H}$ = 6.6 Hz, 1 H), 4.09 (dt, $J_{H,H}$ = 3.2, $J_{H,H}$ = 9.0 Hz, 1 H), 3.26 (dt, $J_{H,H}$ = 3.4, $J_{H,H}$ = 13.7 Hz, 1 H), 2.88 (dd, $J_{H,H}$ = 2.2, $J_{H,H}$ = 3.2 Hz, 1 H), 2.22–2.28 (m, 3 H), 2.12 (m, 1 H), 1.98 (m, 1 H), 1.75 (m, 1 H), 1.41–1.59 (m, 3 H), 1.22 (d, $J_{H,H}$ = 6.6 Hz, 3 H), 1.12–1.39 (m, 6 H), 0.94 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 172.2, 166.1, 65.6, 59.6, 52.9, 34.7, 32.9, 32.7, 25.6, 25.4, 25.3, 25.2, 19.0, 18.5, 13.9 ppm. HRMS (TOF MS ES$^+$): calcd. for $C_{16}H_{25}NO_4$ 318.1681 [M + Na]$^+$; found 318.1693. IR (NaCl): $\tilde{\nu}_{max}$ = 2866–2930, 1796, 1726, 1701 cm^{-1}.

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-(prop-2-enyl)-4-propyl-2-azetidinone (9a): KOH (155 mg, 2.77 mmol, 1.5 equiv.), KI (613 mg, 3.70 mmol, 2 equiv.), Bu_4NHSO_4 (25 mg, 0.074 mmol, 0.04 equiv.) and allyl bromide (0.48 mL, 5.53 mmol, 3 equiv.) were added to a stirred solution of β-lactam **3** (500 mg, 1.85 mmol) in anhydrous THF (10 mL). The reaction was performed at room temp. under argon for 15 h. Then the reaction medium was filtered and the solvent removed under reduced pressure. The crude product was directly purified by flash chromatography (CyHex/AcOEt, 5:2) to provide **9a** as a yellow oil (535 mg, 93%). TLC (CyHex/AcOEt, 5:2): R_f = 0.59. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 5.58–5.79 (ddt, $J_{H,H}$ = 6.1, $J_{H,H}$ = 10.2, $J_{H,H}$ = 16.8 Hz, 1 H), 5.20 (dd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 16.8 Hz, 1 H), 5.05 (dd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 10.0 Hz, 1 H), 4.09 (qd, $J_{H,H}$ = 4.6, $J_{H,H}$ = 6.2 Hz, 1 H), 3.85–3.96 (ddd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 5.4, $J_{H,H}$ = 15.7 Hz, 1 H), 3.60 (m, 2 H), 2.62 (dd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 4.5 Hz, 1 H), 1.65 (m, 1 H), 1.40 (m, 3 H), 1.12 (d, $J_{H,H}$ = 6.2 Hz, 3 H), 0.88 (t, $J_{H,H}$ = 6.8 Hz, 3 H), 0.80 (s, 9 H), 0.00 (2 s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 167.8, 132.7, 117.9, 65.4, 63.2, 54.1, 43.0, 35.0, 25.8, 22.8, 19.3, 17.9, 14.2, –4.5, –4.8 ppm. HRMS (TOF MS ES$^+$): calcd. for $C_{17}H_{33}NO_2Si$ 334.2178 [M + Na]$^+$; found 334.2188. IR (NaCl): $\tilde{\nu}_{max}$ = 2856–2958, 1756, 1645, 1320, 836 cm^{-1}.

(3*S*,4*R*)-1-(But-3-enyl)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-propyl-2-azetidinone (9b): The *N*-(but-3-enyl) derivative was obtained according to the procedure described above for the synthesis of compound **9a** from β-lactam **3** (1 g, 3.69 mmol). Flash chromatography (CyHex/AcOEt, 5:2) provided **9b** as a yellow oil (828 mg, 69%). TLC (CyHex/AcOEt, 5:2): R_f = 0.60. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 5.66–5.84 (ddt, $J_{H,H}$ = 6.8, $J_{H,H}$ = 10.1, $J_{H,H}$ = 17.0 Hz, 1 H), 5.0–5.2 (m, 2 H), 4.09 (qd, $J_{H,H}$ = 5.4, $J_{H,H}$ = 6.1 Hz, 1 H), 3.55 (m, 1 H), 3.3–3.5 (m, 1 H), 2.9–3.1 (m, 1 H), 2.64 (dd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 5.4 Hz, 1 H), 2.28 (td, $J_{H,H}$ = 6.6, $J_{H,H}$ = 7.3 Hz, 2 H), 1.65 (m, 1 H), 1.40 (m, 3 H), 1.19 (d, $J_{H,H}$ = 6.2 Hz, 3 H), 0.96 (t, $J_{H,H}$ = 6.8 Hz, 3 H), 0.86 (s, 9 H), 0.04 and 0.06 (2 s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 168.0, 135.2, 116.9, 65.9, 63.0, 54.6, 39.5, 35.0, 32.8, 25.7, 22.9, 19.3, 17.9, 14.3, –4.5, –4.7 ppm. HRMS (TOF MS ES$^+$): calcd. for $C_{18}H_{35}NO_2Si$ 348.2335 [M + Na]$^+$; found 348.2321. IR (NaCl): $\tilde{\nu}_{max}$ = 2853–2958, 1750, 1640, 833 cm^{-1}.

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(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-(pent-4-enyl)-4-propyl-2-azetidinone (9c): The *N*-(pent-4-enyl) derivative was obtained according to the procedure described above for the synthesis of compound **9a** from β-lactam **3** (400 mg, 1.75 mmol). Flash chromatography (CyHex/AcOEt, 5:2) provided **9c** as a yellow oil (384 mg, 74%). TLC (CyHex/AcOEt, 5:2): R_f = 0.65. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 5.65–5.85 (ddt, $J_{H,H}$ = 6.5, $J_{H,H}$ = 10.1, $J_{H,H}$ = 16.8 Hz, 1 H), 5.02 (m, 1 H), 4.94 (m, 1 H), 4.10 (qd, $J_{H,H}$ = 5.1, $J_{H,H}$ = 6.1 Hz, 1 H), 3.51 (m, 1 H), 3.29 (m, 1 H), 2.93 (m, 1 H), 2.62 (dd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 5.1 Hz, 1 H), 2.0 (m, 2 H), 1.28–1.60 (m, 6 H), 1.16 (d, $J_{H,H}$ = 6.2 Hz, 3 H), 0.93 (t, $J_{H,H}$ = 6.8 Hz, 3 H), 0.83 (s, 9 H), 0.02 and 0.03 (2 s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 167.9, 137.4, 115.2, 65.5, 62.8, 54.2, 39.6, 34.9, 31.1, 27.4, 25.7, 22.8, 19.3, 17.8, 14.2, –4.6, –4.8 ppm. HRMS (TOF MS ES$^+$): calcd. $C_{19}H_{37}NO_2Si$ 362.2491 $[M + Na]^+$; found 362.2477. IR (NaCl): $\tilde{\nu}_{max}$ = 2856–2956, 1753, 1641, 836 cm^{-1}.

(3*S*,4*R*)-3-[(1*R*)-1-Hydroxyethyl]-1-(prop-2-enyl)-4-propyl-2-azetidinone (10a): The *O*-deprotected β-lactam **10a** was obtained according to the procedure described above for the synthesis of compound **5** from β-lactam **9a** (1.48 g, 4.76 mmol) in 96% yield (900 mg) as a pale-yellow oil and was used in the next step without purification. TLC (CyHex/AcOEt, 5:4): R_f = 0.20. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 5.70 (ddt, $J_{H,H}$ = 6.6, $J_{H,H}$ = 10.2, $J_{H,H}$ = 17.5 Hz, 1 H), 5.22 (dd, $J_{H,H}$ = 1.4, $J_{H,H}$ = 17.5 Hz, 1 H), 5.08 (dd, $J_{H,H}$ = 1.3, $J_{H,H}$ = 10.2 Hz, 1 H), 4.07 (qd, $J_{H,H}$ = 5.4, $J_{H,H}$ = 6.3 Hz, 1 H), 3.95 (dd, $J_{H,H}$ = 6.6, $J_{H,H}$ = 15.9 Hz, 1 H), 3.53 (m, 3 H), 2.70 (dd, $J_{H,H}$ = 1.9, $J_{H,H}$ = 5.1 Hz, 1 H), 1.65 (m, 1 H), 1.20–1.40 (m, 3 H), 1.20 (d, $J_{H,H}$ = 6.3 Hz, 3 H), 0.89 (t, $J_{H,H}$ = 6.7 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 168.0, 132.1, 117.8, 64.6, 62.6, 54.3, 42.9, 34.8, 21.6, 19.2, 14.2 ppm. MS (CI, CH_4/NO_2): *m*/*z* = 198.1 $[M^+ H]^+$ for $C_{11}H_{19}NO_2$.

(3*S*,4*R*)-1-(But-3-enyl)-3-[(1*R*)-1-hydroxyethyl]-4-propyl-2-azetidinone (10b): The *O*-deprotected β-lactam **10b** was obtained according to the procedure described above for the synthesis of compound **5** from β-lactam **9b** (1.15 g, 3.54 mmol) in 82% yield (613 mg) as a yellow oil and was used in the next step without purification. TLC (CyHex/AcOEt, 5:4): R_f = 0.21. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 5.72 (ddt, $J_{H,H}$ = 6.7, $J_{H,H}$ = 10.3, $J_{H,H}$ = 17.0 Hz, 1 H), 5.09 (dd, $J_{H,H}$ = 1.6, $J_{H,H}$ = 17.0 Hz, 1 H), 4.98 (dd, $J_{H,H}$ = 1.6, $J_{H,H}$ = 10.3 Hz, 1 H), 4.05 (qd, $J_{H,H}$ = 5.4, $J_{H,H}$ = 6.4 Hz, 1 H), 3.55 (m, 1 H), 3.40 (m, 1 H), 2.90 (m, 1 H), 2.70 (br. s, 1 H), 2.68 (dd, $J_{H,H}$ = 2.0, $J_{H,H}$ = 5.2 Hz, 1 H), 2.24 (m, 2 H), 1.70 (m, 1 H), 1.40 (m, 3 H), 1.20 (d, $J_{H,H}$ = 6.7 Hz, 3 H), 0.92 (t, $J_{H,H}$ = 7.1 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 167.9, 134.8, 116.8, 64.8, 62.4, 54.4, 39.5, 34.7, 32.4, 21.5, 19.1, 14.2 ppm. MS (CI, CH_4/NO_2): *m*/*z* = 212.2 $[M + H]^+$ for $C_{12}H_{21}NO_2$.

(3*S*,4*R*)-3-[(1*R*)-1-Hydroxyethyl]-1-(pent-4-enyl)-4-propyl-2-azetidinone (10c): The *O*-deprotected β-lactam **10c** was obtained according to the procedure described above for the synthesis of compound **5** from β-lactam **9c** (2.09 g, 6.16 mmol) in 100% yield (1.39 g) as a yellow oil and was used in the next step without purification. TLC (CyHex/AcOEt, 5:4): R_f = 0.22. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 5.76 (ddt, $J_{H,H}$ = 6.6, $J_{H,H}$ = 10.2, $J_{H,H}$ = 16.8 Hz, 1 H), 5.05 (dd, $J_{H,H}$ = 1.7, $J_{H,H}$ = 16.8 Hz, 1 H), 4.94 (dd, $J_{H,H}$ = 1.7, $J_{H,H}$ = 10.2 Hz, 1 H), 4.12 (qd, $J_{H,H}$ = 5.5, $J_{H,H}$ = 6.3 Hz, 1 H), 3.55 (m, 1 H), 3.35 (m, 1 H), 2.95 (m, 1 H), 2.72 (dd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 5.1 Hz, 1 H), 2.44 (br. s, 1 H), 2.08 (td, $J_{H,H}$ = 6.6, $J_{H,H}$ = 7.0 Hz, 2 H), 1.30–1.80 (2 m, 6 H), 1.24 (d, $J_{H,H}$ = 6.4 Hz, 3 H), 0.95 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 168.0, 137.2, 115.2, 64.6, 62.3, 54.2, 39.6, 34.8, 31.0, 27.2, 21.6, 19.2, 14.2 ppm. MS (CI, CH_4/NO_2): *m*/*z* = 226.2 $[M + H]^+$ for $C_{13}H_{23}NO_2$.

(3*S*,4*R*)-3-[(1*R*)-1-(Pent-4-enoyloxy)ethyl]-1-(prop-2-enyl)-4-propyl-2-azetidinone (11a): The *O*-acylated β-lactam **11a** was obtained according to the procedure described above for the synthesis of compound **6** from β-lactam **10a** (900 mg, 4.57 mmol). Flash chromatography (CyHex/AcOEt, 5:2) provided the desired compound as a yellow oil (1.065 g, 83%). TLC (CyHex/AcOEt, 5:2): R_f = 0.58. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.79 (ddt, $J_{H,H}$ = 5.1, $J_{H,H}$ = 10.4, $J_{H,H}$ = 17.3 Hz, 1 H), 5.73 (m, 1 H), 5.22 (dddd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 17.2 Hz, 1 H), 5.18 (m, 1 H), 5.17 (m, 1 H), 5.04 (ddt, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 17.3 Hz, 1 H), 4.99 (ddt, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 10.4 Hz, 1 H), 4.02 (dddd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 5.1, $J_{H,H}$ = 15.8 Hz, 1 H), 3.55 (dddd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 6.9, $J_{H,H}$ = 15.8 Hz, 1 H), 3.45 (ddd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 4.3, $J_{H,H}$ = 8.4 Hz, 1 H), 2.85 (dd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 8.0 Hz, 1 H), 2.35 (m, 4 H), 1.73 (m, 1 H), 1.38 (m, 3 H), 1.34 (d, $J_{H,H}$ = 6.2 Hz, 3 H), 0.93 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 172.0, 165.9, 136.4, 132.0, 118.1, 115.4, 68.5, 60.3, 55.6, 42.7, 34.6, 33.6, 28.6, 18.8, 18.6, 14.0 ppm. HRMS (TOF MS ES+): calcd. for $C_{16}H_{25}NO_3$ 280.1913 $[M + H]^+$; found 280.1925. IR (NaCl): $\tilde{\nu}_{max}$ = 3080, 2874–2958, 1755, 1740, 1642 cm^{-1}.

(3*S*,4*R*)-1-(But-3-enyl)-3-[(1*R*)-1-(pent-4-enoyloxy)ethyl]-4-propyl-2-azetidinone (11b): The *O*-acylated β-lactam **11b** was obtained according to the procedure described above for the synthesis of compound **6** from β-lactam **10b** (350 mg, 1.66 mmol). Flash chromatography (CyHex/AcOEt, 5:1) provided the desired compound as a pale-yellow oil (440 mg, 90%). TLC (CyHex/AcOEt, 5:2): R_f = 0.48. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.76 (m, 1 H), 5.72 (ddt, $J_{H,H}$ = 6.7, $J_{H,H}$ = 10.2, $J_{H,H}$ = 17.1 Hz, 1 H), 5.11 (m, 1 H), 5.08 (m, 1 H), 5.04 (m, 1 H), 5.01 (m, 1 H), 4.97 (dd, $J_{H,H}$ = 1.6, $J_{H,H}$ = 10.1 Hz, 1 H), 3.43 (m, 1 H), 3.40 (m, 1 H), 2.97 (m, 1 H), 2.78 (dd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 8.1 Hz, 1 H), 2.32 (m, 4 H), 2.24 (m, 2 H), 1.71 (m, 1 H), 1.35 (m, 2 H), 1.30 (d, $J_{H,H}$ = 6.4 Hz, 3 H), 1.27 (m, 1 H), 0.93 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 171.9, 165.8, 136.3, 134.6, 117.0, 115.3, 68.7, 60.1, 55.6, 39.2, 34.5, 33.5, 32.2, 28.6, 18.7, 18.5, 13.9 ppm. HRMS (TOF MS ES+): calcd. for $C_{17}H_{27}NO_3$ 294.2069 $[M + H]^+$; found 294.2064. IR (NaCl): $\tilde{\nu}_{max}$ = 3077, 2873–2958, 1752, 1740, 1641 cm^{-1}.

(3*S*,4*R*)-3-[(1*R*)-1-(Pent-4-enoyloxy)ethyl]-1-(pent-4-enyl)-4-propyl-2-azetidinone (11c): The *O*-acylated β-lactam **11c** was obtained according to the procedure described above for the synthesis of compound **6** from β-lactam **10c** (300 mg, 1.33 mmol). Flash chromatography (CyHex/AcOEt, 5:2) provided the desired compound as a pale-yellow oil (375 mg, 92%). TLC (CyHex/AcOEt, 1:1): R_f = 0.76. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.78 (m, 2 H), 5.16 (qd, $J_{H,H}$ = 6.3, $J_{H,H}$ = 8.0 Hz, 1 H), 5.04 (ddd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 17.3 Hz, 1 H), 5.03 (ddd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 17.3 Hz, 1 H), 5.00 (ddd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 10.4 Hz, 1 H), 4.99 (ddd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 10.4 Hz, 1 H), 3.42 (ddd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 4.3, $J_{H,H}$ = 8.3 Hz, 1 H), 3.37 (dt, $J_{H,H}$ = 7.6, $J_{H,H}$ = 14.3 Hz, 1 H), 2.94 (dt, $J_{H,H}$ = 7.6, $J_{H,H}$ = 14.3 Hz, 1 H), 2.82 (dd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 8.0 Hz, 1 H), 2.35 (m, 4 H), 2.07 (m, 2 H), 1.75 (m, 1 H), 1.62 (m, 2 H), 1.38 (m, 2 H), 1.34 (d, $J_{H,H}$ = 6.3 Hz, 3 H), 1.29 (m, 1 H), 0.95 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 172.0, 166.0, 137.1, 136.4, 115.4, 115.3, 68.6, 60.1, 55.5, 39.5, 34.6, 33.6, 30.9, 28.7, 27.1, 18.8, 18.6, 14.0 ppm. HRMS (TOF MS ES+): calcd. for $C_{18}H_{29}NO_3$ 330.2045 $[M + Na]^+$; found 330.2056. IR (NaCl): $\tilde{\nu}_{max}$ = 3078, 2874–2958, 1754, 1745, 1641 cm^{-1}.

(10*R*,11*S*,13*R*)-10-Methyl-8,12-dioxo-13-propyl-9-oxa-1-azabicyclo-[9.1.1]tridec-4-ene (12b). Method B: Ti(O*i*Pr)$_4$ (20 mol-%) was in-

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jected into a stirred solution of precursor **11b** (415 mg, 1.42 mmol) in anhydrous toluene (5 mM) under argon. The temperature was raised to 80 °C and Grubbs catalyst (2.5 mol-%) was added. The reaction was performed at this temperature for 24 h. Then the reaction medium was filtered through Celite and the solvent removed under reduced pressure. The dark residue was purified by flash chromatography (CyHex/AcOEt, 5:3) to provide the cyclized compound **12b** as a white solid (280 mg, 74%) in a stereoisomeric ratio of 75:25. TLC (CyHex/AcOEt, 5:3): R_f = 0.18. GC: t_r = 35.4 min. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, major isomer): δ = 5.48 (m, 1 H), 5.46 (m, 1 H), 5.33 (m, 1 H), 3.75 (m, 1 H), 3.68 (m, 1 H), 2.88 (m, 1 H), 2.80 (br. s, 1 H), 2.47 (m, 1 H), 2.36 (m, 3 H), 2.22 (m, 2 H), 1.77 (m, 1 H), 1.43 (m, 3 H), 1.24 (d, $J_{H,H}$ = 6.9 Hz, 3 H), 1.02 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 171.4, 167.0, 132.7, 128.2, 64.3, 60.1, 51.8, 38.6, 35.2, 34.7, 31.3, 29.0, 19.7, 19.6, 14.3 ppm. HRMS (TOF MS ES+): calcd. for $C_{15}H_{23}NO_3$ 266.1756 $[M + H]^+$; found 266.1747. IR (NaCl): $\tilde{\nu}_{max}$ = 2858–2959, 1763, 1728 cm^{-1}.

(11*R*,12*S*,14*R*)-11-Methyl-9,13-dioxo-14-propyl-10-oxa-1-azabicyclo[10.1.1]tetradec-5-ene (12c): The cyclized compound **12c** was obtained from precursor **11c** by using Method B (395 mg, 1.29 mmol) with 5 mol-% of Grubbs catalyst. After 19.5 h and the usual workup, flash chromatography (CyHex/AcOEt, 5:3) provided the desired β-lactam (220 mg, 62%) as a mixture of **12c** and **12b** in a 75:25 ratio. TLC (CyHex/AcOEt, 5:3): R_f = 0.16. GC: t_r = 37.0 min. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, major isomer): δ = 5.43 (m, 3 H), 3.67 (m, 1 H), 3.55 (m, 1 H), 2.88 (m, 1 H), 2.72 (br. s, 1 H), 2.47 (m, 2 H), 1.5–2.4 (5 m, 7 H), 1.36 (m, 3 H), 1.20 (d, $J_{H,H}$ = 6.4 Hz, 3 H), 0.97 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 171.7, 165.9, 129.5, 128.4, 65.1, 59.9, 52.4, 40.2, 33.8, 32.9, 32.4, 26.9, 25.5, 19.2, 19.0, 14.2 ppm. HRMS (TOF MS ES+): calcd. for $C_{16}H_{25}NO_3$ 280.1913 $[M + H]^+$; found 280.1901. IR (NaCl): $\tilde{\nu}_{max}$ = 2858–2957, 1751 cm^{-1}.

(10*R*,11*S*,13*R*)-10-Methyl-8,12-dioxo-13-propyl-9-oxa-1-azabicyclo[9.1.1]tridecane (13b): Compound **13b** was quantitatively obtained as a white solid from the cyclized β-lactam **12b** (400 mg, 1.51 mmol) by using the procedure described above for the synthesis of compound **3**. TLC (CyHex/AcOEt, 5:4): R_f = 0.33. M.p. 70.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.38 (qd, $J_{H,H}$ = 0.9, $J_{H,H}$ = 6.4 Hz, 1 H), 3.67 (m, 1 H), 3.44 (m, 1 H), 2.79 (m, 1 H), 2.65 (br. s, 1 H), 2.40 (m, 1 H), 2.12 (m, 1 H), 1.69 (m, 1 H), 1.37 (m, 3 H), 1.18–1.75 (m, 8 H), 1.14 (d, $J_{H,H}$ = 6.4 Hz, 3 H), 0.88 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 171.0, 166.1, 64.6, 60.0, 52.4, 38.5, 34.3, 34.0, 26.3, 24.5, 22.8, 22.5, 19.2, 19.0, 14.0 ppm. HRMS (TOF MS ES+): calcd. for $C_{15}H_{25}NO_3$ 268.1913 $[M + H]^+$; found 268.1914. IR (NaCl): $\tilde{\nu}_{max}$ = 2858–2959, 1755, 1736 cm^{-1}.

(11*R*,12*S*,14*R*)-11-Methyl-9,13-dioxo-14-propyl-10-oxa-1-azabicyclo[10.1.1]tetradecane (13c): Compound **13c** was quantitatively obtained as a white gum from the cyclized β-lactam **12c** (70 mg, 0.26 mmol) by using the procedure described above for the synthesis of compound **3**. TLC (CyHex/AcOEt, 5:3): R_f = 0.30. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.36 (qd, $J_{H,H}$ = 2.0, $J_{H,H}$ = 6.6 Hz, 1 H), 3.74 (m, 1 H), 3.54 (m, 1 H), 2.80 (dd, $J_{H,H}$ = 1.9, $J_{H,H}$ = 2.0 Hz, 1 H), 2.76 (m, 1 H), 2.31 (t, $J_{H,H}$ = 5.9 Hz, 2 H), 1.26–1.83 (m, 14 H), 1.24 (d, $J_{H,H}$ = 6.6 Hz, 3 H), 0.98 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 172.5, 166.7, 65.6, 60.0, 53.5, 40.2, 34.4, 33.6, 26.8, 26.4, 25.8, 25.4, 23.6, 19.2, 19.1, 14.2 ppm. HRMS (TOF MS ES+): calcd. for $C_{16}H_{27}NO_3$ 304.1889 $[M + Na]^+$; found 304.1889. IR (NaCl): $\tilde{\nu}_{max}$ = 2860–2930, 1751 cm^{-1}.

(3*S*,4*R*)-1-(Prop-2-enyl)-3-[(1*R*)-1-(prop-2-enyloxy)ethyl]-4-propyl-2-azetidinone (14a): NaH (60% dispersion in oil, 83 mg, 1.72 mmol, 1.1 equiv.) was added to a stirred solution of β-lactam **10a** (306 mg, 1.56 mmol) in dry DMF (10 mL) at 0 °C under argon. After 20 min, KI (702 mg, 4.68 mmol, 3 equiv.) and allyl bromide (0.40 mL, 4.68 mmol, 3 equiv.) were added, and the temperature of the reaction medium was allowed to slowly rise to room temp. After 6 h, a saturated solution of NH_4Cl was injected dropwise and the medium diluted with diethyl ether (50 mL). The organic layer was washed three times with brine, dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (CyHex/AcOEt, 5:2) to provide **14a** as a pale-yellow oil (254 mg, 69%). TLC (CyHex/AcOEt, 5:2): R_f = 0.45. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.84 (dddd, $J_{H,H}$ = 5.4, $J_{H,H}$ = 5.4, $J_{H,H}$ = 10.4, $J_{H,H}$ = 17.3 Hz, 1 H), 5.71 (dddd, $J_{H,H}$ = 5.1, $J_{H,H}$ = 6.9, $J_{H,H}$ = 10.4, $J_{H,H}$ = 17.3 Hz, 1 H), 5.22 (m, 2 H), 5.14 (ddd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.8, $J_{H,H}$ = 10.4 Hz, 1 H), 5.10 (dddd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 10.4 Hz, 1 H), 4.06 (dddd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 5.4, $J_{H,H}$ = 12.7 Hz, 1 H), 4.02 (dddd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 1.8, $J_{H,H}$ = 5.1, $J_{H,H}$ = 15.8 Hz, 1 H), 3.92 (dddd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 5.4, $J_{H,H}$ = 12.7 Hz, 1 H), 3.76 (qd, $J_{H,H}$ = 5.8, $J_{H,H}$ = 6.3 Hz, 1 H), 3.57 (ddd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 4.3, $J_{H,H}$ = 8.3 Hz, 1 H), 3.52 (dd, $J_{H,H}$ = 6.9, $J_{H,H}$ = 15.8 Hz, 1 H), 2.72 (dd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 5.8 Hz, 1 H), 1.70 (m, 1 H), 1.35 (m, 3 H), 1.21 (d, $J_{H,H}$ = 6.3 Hz, 3 H), 0.91 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 167.6, 134.9, 132.1, 117.6, 116.3, 71.9, 69.8, 61.5, 54.7, 42.6, 34.7, 18.9, 18.4, 14.0 ppm. HRMS (TOF MS ES+): calcd. for $C_{14}H_{23}NO_2$ 238.1807 $[M + H]^+$; found 238.1809. IR (NaCl): $\tilde{\nu}_{max}$ = 2931–2961, 1750, 1641 cm^{-1}.

(3*S*,4*R*)-3-[(1*R*)-1-(Pent-4-enyloxy)ethyl]-1-(prop-2-enyl)-4-propyl-2-azetidinone (14b): The *O*-(pent-4-enyl) derivative was obtained according to the procedure described above for the synthesis of compound **14a** from β-lactam **10a** (779 mg, 3.95 mmol) and 4-pentenyl bromide. Flash chromatography (CyHex/AcOEt, 5:2) provided **14b** as a pale-yellow oil (394 mg, 38%). TLC (CyHex/AcOEt, 5:2): R_f = 0.50. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.73 (ddt, $J_{H,H}$ = 6.7, $J_{H,H}$ = 10.2, $J_{H,H}$ = 17.0 Hz, 1 H), 5.66 (ddt, $J_{H,H}$ = 6.7, $J_{H,H}$ = 10.2, $J_{H,H}$ = 17.0 Hz, 1 H), 5.19 (dd, $J_{H,H}$ = 1.2, $J_{H,H}$ = 17.0 Hz, 1 H), 5.10 (dd, $J_{H,H}$ = 1.2, $J_{H,H}$ = 10.2 Hz, 1 H), 4.94 (dd, $J_{H,H}$ = 1.0, $J_{H,H}$ = 17.0 Hz, 1 H), 4.88 (dd, $J_{H,H}$ = 1.0, $J_{H,H}$ = 10.2 Hz, 1 H), 3.98 (dd, $J_{H,H}$ = 6.7, $J_{H,H}$ = 15.9 Hz, 1 H), 3.64 (qd, $J_{H,H}$ = 5.8, $J_{H,H}$ = 6.2 Hz, 1 H), 3.50 (m, 3 H), 3.28 (m, 3 H), 2.67 (dd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 5.8 Hz, 1 H), 2.03 (td, $J_{H,H}$ = 6.7, $J_{H,H}$ = 7.3 Hz, 2 H), 1.67 (m, 1 H), 1.55 (quint, $J_{H,H}$ = 7.3 Hz, 3 H), 1.31 (m, 3 H), 1.16 (d, $J_{H,H}$ = 6.2 Hz, 3 H), 0.88 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 167.7, 138.0, 132.1, 117.5, 114.4, 72.3, 68.0, 61.5, 54.6, 42.4, 34.6, 30.0, 29.0, 18.9, 18.2, 13.9 ppm. HRMS (TOF MS ES+): calcd. for $C_{16}H_{27}NO_2$ 288.1939 $[M + Na]^+$; found 288.1942. IR (NaCl): $\tilde{\nu}_{max}$ = 3077, 2871–2931, 1750, 1637 cm^{-1}.

(3*S*,4*R*)-1-(But-3-enyl)-3-[(1*R*)-1-(pent-4-enyloxy)ethyl]-4-propyl-2-azetidinone (15b): The *O*-(pent-4-enyl) derivative was synthesized according to the procedure described above for the synthesis of compound **14a** from β-lactam **10b** (260 mg, 1.23 mmol), with NaH added in portions (3 × 1.1 equiv.), pent-4-enyl bromide and no KI. Flash chromatography (CyHex/AcOEt, 5:1) provided **15b** as a pale-yellow oil (240 mg, 70%). TLC (CyHex/AcOEt, 5:2): R_f = 0.56. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.77 (ddt, $J_{H,H}$ = 6.6, $J_{H,H}$ = 10.2, $J_{H,H}$ = 16.9 Hz, 1 H), 5.73 (ddt, $J_{H,H}$ = 6.7, $J_{H,H}$ = 10.2, $J_{H,H}$ = 17.1 Hz, 1 H), 5.06 (dd, $J_{H,H}$ = 1.7, $J_{H,H}$ = 17.1 Hz, 1 H), 5.01 (dd, $J_{H,H}$ = 1.7, $J_{H,H}$ = 10.2 Hz, 1 H), 4.96 (dd, $J_{H,H}$ = 2.0, $J_{H,H}$ = 16.9 Hz, 1 H), 4.91 (dd, $J_{H,H}$ = 2.0, $J_{H,H}$ = 10.2 Hz, 1 H), 3.61

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(qd, $J_{H,H}$ = 6.3, $J_{H,H}$ = 6.4 Hz, 1 H), 3.52 (m, 1 H), 3.50 (m, 1 H), 3.45 (m, 1 H), 3.30 (m, 1 H), 2.95 (m, 1 H), 2.65 (dd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 6.4 Hz, 1 H), 2.25 (m, 2 H), 2.05 (m, 2 H), 1.71 (m, 1 H), 1.57 (quint, $J_{H,H}$ = 7.3 Hz, 2 H), 1.35 (m, 3 H), 1.18 (d, $J_{H,H}$ = 6.2 Hz, 3 H), 0.93 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 167.8, 138.2, 135.0, 116.8, 114.6, 72.9, 68.0, 61.4, 55.0, 39.3, 34.7, 32.4, 30.2, 29.1, 19.0, 18.4, 14.1 ppm. HRMS (TOF MS ES+): calcd. for $C_{17}H_{29}NO_2$ 280.2276 [M + Na]$^+$; found 280.2273.

(3*S*,4*R*)-1-(Pent-4-enyl)-3-[(1*R*)-1-(prop-2-enyloxy)ethyl]-4-propyl-2-azetidinone (16a): The *O*-(prop-2-enyl) derivative was obtained according to the procedure described above for the synthesis of compound **14a** from β-lactam **10c** (405 mg, 1.8 mmol) and allyl bromide. Flash chromatography (CyHex/AcOEt, 5:3) provided **16a** as a pale-yellow oil (408 mg, 85%). TLC (CyHex/AcOEt, 5:2): R_f = 0.43. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.80 (ddt, $J_{H,H}$ = 5.4, $J_{H,H}$ = 10.4, $J_{H,H}$ = 17.3 Hz, 1 H), 5.72 (ddt, $J_{H,H}$ = 6.5, $J_{H,H}$ = 10.4, $J_{H,H}$ = 17.3 Hz, 1 H), 5.18 (ddt, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 17.3 Hz, 1 H), 5.06 (ddt, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 10.4 Hz, 1 H), 4.96 (ddt, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 17.3 Hz, 1 H), 4.91 (ddt, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 10.4 Hz, 1 H), 4.02 (dddd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 5.4, $J_{H,H}$ = 12.7 Hz, 1 H), 3.88 (dddd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 1.5, $J_{H,H}$ = 5.4, $J_{H,H}$ = 12.7 Hz, 1 H), 3.71 (qd, $J_{H,H}$ = 5.8, $J_{H,H}$ = 6.3 Hz, 1 H), 3.49 (m, 1 H), 3.33 (td, $J_{H,H}$ = 7.9, $J_{H,H}$ = 14.3 Hz, 1 H), 2.88 (td, $J_{H,H}$ = 7.6, $J_{H,H}$ = 14.3 Hz, 1 H), 2.65 (dd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 5.8 Hz, 1 H), 2.02 (m, 2 H), 1.69 (m, 1 H), 1.56 (m, 2 H), 1.33 (m, 3 H), 1.17 (d, $J_{H,H}$ = 6.3 Hz, 3 H), 0.90 (t, $J_{H,H}$ = 7.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 167.5, 137.2, 134.8, 116.2, 115.0, 71.8, 69.7, 61.1, 54.4, 39.1, 34.6, 30.7, 26.9, 18.9, 18.3, 13.9 ppm. HRMS (TOF MS ES+): calcd. for $C_{16}H_{27}NO_2$ 288.1939 [M + Na]$^+$; found 288.1928. IR (NaCl): $\tilde{\nu}_{max}$ = 2872–2959, 1749, 1641 cm^{-1}.

(3*S*,4*R*)-1-(Pent-4-enyl)-3-[(1*R*)-1-(pent-4-enyloxy)ethyl]-4-propyl-2-azetidinone (16b): The *O*-(pent-4-enyl) derivative was obtained according to the procedure described above for the synthesis of compound **14a** from β-lactam **10c** (300 mg, 1.34 mmol), with NaH added in portions (3 × 1.1 equiv.), 4-pentenyl bromide and no KI. Flash chromatography (CyHex/AcOEt, 5:2) provided **16b** as a pale-yellow oil (269 mg, 68%). TLC (CyHex/AcOEt, 5:2): R_f = 0.50. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.77 (m, 2 H), 5.01 (m, 1 H), 4.98 (m, 1 H), 4.96 (m, 1 H), 4.92 (m, 1 H), 3.67 (qd, $J_{H,H}$ = 5.7, $J_{H,H}$ = 6.2 Hz, 1 H), 3.54 (m, 1 H), 3.52 (m, 1 H), 3.37 (m, 1 H), 3.32 (m, 1 H), 2.91 (m, 1 H), 2.67 (dd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 5.7 Hz, 1 H), 2.07 (m, 4 H), 1.72 (m, 1 H), 1.59 (m, 4 H), 1.37 (m, 3 H), 1.19 (d, $J_{H,H}$ = 6.2 Hz, 3 H), 0.94 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 167.8, 138.2, 137.3, 115.1, 114.5, 72.5, 68.1, 61.3, 54.5, 39.3, 34.7, 30.8, 30.1, 29.1, 27.1, 19.0, 18.3, 14.1 ppm. HRMS (TOF MS ES+): calcd. $C_{18}H_{31}NO_2$ 316.2252 [M + Na]$^+$; found 316.2250. IR (NaCl): $\tilde{\nu}_{max}$ = 3077, 2872–2958, 1749, 1641 cm^{-1}.

(10*R*,11*S*,13*R*)-10-Methyl-12-oxo-13-propyl-9-oxa-1-azabicyclo[9.1.1]tridec-4-ene (17b): The cyclized compound **17b** was obtained from the corresponding precursor **15b** (530 mg, 1.9 mmol) by using Method B with 5 mol-% of Grubbs catalyst. After 24 h and the usual workup, flash chromatography (CyHex/AcOEt, 5:1) provided the desired β-lactam (395 mg, 83%) as a mixture of stereoisomers in a 73:27 ratio. TLC (CyHex/AcOEt, 5:4): R_f = 0.37. GC: t_r = 31.2 min. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C; major isomer): δ = 5.03–5.37 (m, 2 H), 3.47–3.60 (m, 4 H), 3.32 (m, 1 H), 2.71 (m, 1 H), 2.49 (br. s, 1 H), 2.13 (m, 1 H), 2.00 (m, 1 H), 1.88 (m, 1 H), 1.57 (m, 1 H), 1.50 (m, 2 H), 1.24 (m, 3 H), 0.95 (d, $J_{H,H}$ = 6.4 Hz, 3 H), 0.83 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 168.9, 135.6, 124.6, 70.6, 69.6, 60.5, 50.6, 38.6, 34.4, 32.2, 31.1, 28.9, 19.2, 19.1, 14.0 ppm. HRMS (TOF MS ES+): calcd. for $C_{15}H_{25}NO_2$ 252.1964 [M + H]$^+$; found 252.1960. IR (NaCl): $\tilde{\nu}_{max}$ = 2872–2959, 1751 cm^{-1}.

(11*R*,12*S*,14*R*)-11-Methyl-13-oxo-14-propyl-10-oxa-1-azabicyclo[10.1.1]tetradec-5-ene (17c): Cyclized compound **17c** was obtained from precursor **16b** (293 mg, 1 mmol) by using Method B with 5 mol-% of Grubbs catalyst. After 24 h and the usual workup, flash chromatography (CyHex/AcOEt, 5:2) provided the desired β-lactam (190 mg, 72%, white gum) as a mixture of stereoisomers in a ration of 25:75. (*Z*) isomer: TLC (CyHex/AcOEt, 5:4): R_f = 0.45. GC: t_r = 33.5 min. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.33 (m, $J_{H,H}$ = 10.9 Hz, 2 H), 3.85 (qd, $J_{H,H}$ = 1.3, $J_{H,H}$ = 6.6 Hz, 1 H), 3.68 (m, 1 H), 3.60 (m, 1 H), 3.50 (m, 1 H), 3.38 (m, 1 H), 2.75 (m, 1 H), 2.59 (dd, $J_{H,H}$ = 1.3, $J_{H,H}$ = 1.8 Hz, 1 H), 2.37 (m, 2 H), 2.06 (m, 1 H), 1.90 (m, 1 H), 1.67 (m, 1 H), 1.63 (m, 3 H), 1.45 (m, 1 H), 1.36 (m, 1 H), 1.30 (m, 2 H), 1.10 (d, $J_{H,H}$ = 6.6 Hz, 3 H), 0.91 (t, $J_{H,H}$ = 7.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 168.7, 130.1, 128.8, 71.3, 68.5, 61.00, 53.2, 38.1, 34.8, 29.9, 25.9, 23.5, 23.0, 19.7, 19.2, 14.1 ppm. HRMS (EI): calcd. for $C_{16}H_{27}NO_2$ 265.2041; found 265.2039. IR (NaCl): $\tilde{\nu}_{max}$ = 2869–2929, 1747 cm^{-1}. (*E*) isomer: TLC (CyHex/AcOEt, 5:4): R_f = 0.36. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.48 (m, 1 H), 5.38 (m, 1 H), 3.83 (qd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 6.4 Hz, 1 H), 3.73 (m, 1 H), 3.57 (m, 1 H), 3.52 (m, 1 H), 3.47 (m, 1 H), 2.92 (dd, $J_{H,H}$ = 5.9, $J_{H,H}$ = 14.2 Hz, 1 H), 2.56 (d, $J_{H,H}$ = 1.5 Hz, 1 H), 2.05–2.18 (m, 4 H), 1.48–1.75 (m, 5 H), 1.34 (m, 3 H), 1.09 (d, $J_{H,H}$ = 6.4 Hz, 3 H), 0.95 (t, $J_{H,H}$ = 7.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 168.5, 130.1, 129.5, 71.1, 69.4, 60.9, 52.1, 40.1, 34.0, 32.3, 29.8, 27.7, 25.6, 19.7, 19.3, 14.3 ppm.

(10*R*,11*S*,13*R*)-10-Methyl-12-oxo-13-propyl-9-oxa-1-azabicyclo[9.1.1]tridecane (18b): Compound **18b** was quantitatively obtained as a pale-yellow oil from the cyclized β-lactam **17b** (530 mg, 2.11 mmol) by using the procedure described above for the synthesis of compound **3**. TLC (CyHex/AcOEt, 5:4): R_f = 0.60. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.77 (m, 1 H), 3.73 (m, 1 H), 3.40–3.54 (m, 3 H), 2.80 (m, 1 H), 2.51 (br. s, 1 H), 1.65 (m, 1 H), 1.27 (m, 3 H), 1.00–1.75 (several m, 10 H), 1.04 (d, $J_{H,H}$ = 6.9 Hz, 3 H), 0.87 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 168.0, 69.8, 67.5, 60.4, 51.8, 38.9, 33.9, 28.4, 27.2, 23.5, 22.4, 20.0, 19.2, 14.0 ppm. HRMS (TOF MS ES+): calcd. for $C_{15}H_{27}NO_2$ 254.2120 [M + H]$^+$; found 254.2120. IR (NaCl): $\tilde{\nu}_{max}$ = 2860–2926, 1751 cm^{-1}.

(11*R*,12*S*,14*R*)-11-Methyl-13-oxo-14-propyl-10-oxa-1-azabicyclo[10.1.1]tetradecane (18c): Compound **18c** was quantitatively obtained as a yellow gum from the cyclized β-lactam **17c** (120 mg, 0.45 mmol) by using the procedure described above for the synthesis of compound **3**. TLC (CyHex/AcOEt, 5:4): R_f = 0.51. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.79 (qd, $J_{H,H}$ = 2.2, $J_{H,H}$ = 6.4 Hz, 1 H), 3.69 (m, 1 H), 3.61 (m, 1 H), 3.50 (m, 1 H), 3.22 (m, 1 H), 2.72 (m, 1 H), 2.62 (br. s, 1 H), 1.68 (m, 1 H), 1.24–1.61 (m, 13 H), 1.20 (m, 2 H), 1.08 (d, $J_{H,H}$ = 6.4 Hz, 3 H), 0.91 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 168.7, 70.8, 69.6, 61.0, 52.2, 39.3, 34.4, 27.5, 26.3, 25.8, 25.7, 24.1, 19.1, 18.1, 14.0 ppm. HRMS (TOF MS ES+): calcd. for $C_{16}H_{29}NO_2$ 290.2096 [M + Na]$^+$; found 290.2097. IR (NaCl): $\tilde{\nu}_{max}$ = 2858–2955, 1747 cm^{-1}.

Prop-2-enyl 2-{(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxo-4-propyl-1-azetidinyl}acetate (19): NaH (60% dispersion in oil, 85 mg, 2.12 mmol, 1.2 equiv.) was added to a stirred solution of β-lactam **3** (480 mg, 1.77 mmol) in anhydrous DMF (15 mL) at 0 °C under argon. After 15 min, allyl bromoacetate (633 mg, 3.54 mmol, 2 equiv.) was injected and the mixture stirred for 1 h.

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The reaction medium was then diluted with diethyl ether (50 mL) and washed three times with brine. The organic layer was collected, dried with $MgSO_4$, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (CyHex/AcOEt, 5:1) to provide compound **19** as a yellow oil (380 mg, 58%). TLC (CyHex/AcOEt, 5:2): R_f = 0.55. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.84 (ddt, $J_{H,H}$ = 5.9, $J_{H,H}$ = 10.3, $J_{H,H}$ = 17.1 Hz, 1 H), 5.27 (dd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 17.1 Hz, 1 H), 5.20 (dd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 10.3 Hz, 1 H), 4.56 (m, 2 H), 4.09 (qd, $J_{H,H}$ = 6.4, $J_{H,H}$ = 6.4 Hz, 1 H), 4.04 (d, $J_{H,H}$ = 17.9 Hz, 1 H), 3.79 (d, $J_{H,H}$ = 17.9 Hz, 1 H), 3.68 (m, 1 H), 2.70 (dd, $J_{H,H}$ = 2.0, $J_{H,H}$ = 6.4 Hz, 1 H), 1.68 (m, 1 H), 1.42 (m, 1 H), 1.30 (m, 2 H), 1.18 (d, $J_{H,H}$ = 6.4 Hz, 3 H), 0.89 (t, $J_{H,H}$ = 7.3 Hz, 3 H), 0.81 (s, 9 H), 0.00 and 0.01 (2 s, 6 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 168.0, 167.8, 131.3, 118.9, 66.0, 65.8, 63.8, 56.2, 41.6, 34.7, 25.6, 22.7, 19.4, 17.7, 14.1, –4.5, –4.9 ppm. HRMS (TOF MS ES+): calcd. $C_{19}H_{35}NO_4Si$ 370.2414 $[M + H]^+$; found 370.2398.

4-Nitrobenzyl 2-{(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)-ethyl]-2-oxo-4-propyl-1-azetidinyl}pent-4-enoate (21): A freshly prepared solution of LiHMDS (3.52 mmol, 1.2 equiv.) in THF (20 mL) was added to a stirred solution of β-lactam **19** (1.08 g, 2.93 mmol) in THF (9 mL) at –78 °C under argon over 30 min. The solution was stirred for 15 min before the addition of TMSCl (0.38 mL, 2.93 mmol, 1 equiv.). After a further 15 min at this temperature, the reaction medium was heated at reflux for 4 h. The solution was then cooled to 0 °C, and MeOH (5 mL) was added dropwise. After a further 15 min of stirring, the solvents were removed under reduced pressure, and the white paste obtained was dissolved in a 1:1 mixture (100 mL) of diethyl ether/aq. HCl (3.3 M). The organic layer was collected, washed three times with brine, dried with $MgSO_4$, filtered, and the solvent removed to provide a yellow oil (1.15 g). The crude acid **20** (1.08 g, 2.93 mmol) was then stirred in a solution of anhydrous DMF (25 mL) containing K_2CO_3 (606 mg, 4.39 mmol, 1.5 equiv.), Bu_4NHSO_4 (99 mg, 0.293 mmol, 0.1 equiv.) and *p*-nitrobenzyl bromide (1.265 g, 5.86 mmol, 2 equiv.) at room temp. under argon for 21 h. The reaction medium was then diluted with a 1:1 mixture (100 mL) of a diethyl ether/NH_4Cl solution. The organic layer was collected, washed three times with brine (50 mL), dried with $MgSO_4$, filtered, and the solvent removed. The crude product was purified by flash chromatography (CyHex/AcOEt, 5:1) to provide the ester **21** (1.264 g, 86%, yellow oil) as a diastereoisomeric mixture (66:33). A sample of the major diastereoisomer could be isolated for analyses. TLC (CyHex/AcOEt, 5:2): R_f = 0.70. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.25 (d, $J_{H,H}$ = 8.5 Hz, 2 H), 7.55 (d, $J_{H,H}$ = 8.5 Hz, 2 H), 5.80 (ddt, $J_{H,H}$ = 6.8, $J_{H,H}$ = 10.3, $J_{H,H}$ = 17.1 Hz, 1 H), 5.26 (ABq, $J_{H,H}$ = 13.2 Hz, 2 H), 5.20 (dd, $J_{H,H}$ = 1.0, $J_{H,H}$ = 17.1 Hz, 1 H), 5.15 (d, $J_{H,H}$ = 10.3 Hz, 1 H), 4.41 (dd, $J_{H,H}$ = 6.4, $J_{H,H}$ = 6.8 Hz, 1 H), 4.06 (qd, $J_{H,H}$ = 6.4, $J_{H,H}$ = 6.4 Hz, 1 H), 3.60 (m, 1 H), 2.72 (m, 1 H), 2.68 (dd, $J_{H,H}$ = 2.0, $J_{H,H}$ = 6.4 Hz, 1 H), 2.64 (m, 1 H), 1.68 (m, 1 H), 1.34 (m, 3 H), 1.24 (d, 3 H), 0.88 (m, 12 H), 0.04 and 0.07 (2 s, 6 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 169.3, 167.7, 147.4, 142.3, 132.9, 128.5, 123.7, 118.5, 65.9, 65.3, 63.1, 56.8, 54.4, 35.8, 35.6, 25.6, 22.7, 19.3, 17.7, 14.1, –4.6, –4.8 ppm. HRMS (TOF MS ES+): calcd. for $C_{26}H_{40}N_2O_6$ 505.2734 $[M + H]^+$; found 505.2733. IR (NaCl): $\tilde{\nu}_{max}$ = 3080, 2856–2957, 1747, 1643, 1606, 1526, 1348 cm^{-1}. Minor stereoisomer: TLC (CyHex/AcOEt, 5:2): R_f = 0.62.

4-Nitrobenzyl 2-{(3*S*,4*R*)-3-[(1*R*)-1-(Pent-4-enoyloxy)ethyl]-2-oxo-4-propyl-1-azetidinyl}pent-4-enoate (23): After the usual deprotection of the silyl group of β-lactam **21** (745 mg, 1.48 mmol), the free alcohol **22** quantitatively obtained (580 mg, 1.48 mmol) was used without purification in the *O*-acylation step according to the procedure described above for the synthesis of compound **6**. Flash chromatography (CyHex/AcOEt, 5:2) provided the β-lactam **23** as a yellow oil (545 mg, 77%). TLC (CyHex/AcOEt, 5:2): R_f = 0.45. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.22 (d, $J_{H,H}$ = 8.4 Hz, 2 H), 7.53 (d, $J_{H,H}$ = 8.4 Hz, 2 H), 5.75 (ddt, $J_{H,H}$ = 6.4, $J_{H,H}$ = 10.3, $J_{H,H}$ = 17.1 Hz, 2 H), 5.26 (sharp AB q, 2 H), 5.15 (m, 1 H), 5.12 (m, 1 H), 5.10 (m, 1 H), 5.01 (dd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 17.1 Hz, 1 H), 4.99 (dd, $J_{H,H}$ = 1.5, $J_{H,H}$ = 10.3 Hz, 1 H), 4.35 (m, 1 H), 3.61 (m, 1 H), 2.86 (dd, $J_{H,H}$ = 2.0, $J_{H,H}$ = 8.8 Hz, 1 H), 2.66 (m, 2 H), 2.34 (sharp m, 4 H), 1.79 (m, 1 H), 1.23 and 1.40 (2 m, 3 H), 1.32 (d, $J_{H,H}$ = 5.9 Hz, 3 H), 0.91 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 171.9, 169.2, 166.3, 147.7, 142.2, 136.4, 132.7, 128.6, 123.8, 118.7, 115.5, 68.6, 65.6, 60.4, 57.8, 54.5, 35.6, 34.9, 33.5, 28.6, 18.9, 18.6, 14.0 ppm. HRMS (TOF MS ES+): calcd. for $C_{25}H_{32}N_2O_7$ 495.2107 $[M + Na]^+$; found 495.2115. IR (NaCl): $\tilde{\nu}_{max}$ = 3081, 2867–2961, 1737, 1638, 1601, 1523, 1343 cm^{-1}.

4-Nitrobenzyl (10*R*,11*S*,13*R*)-10-Methyl-8,12-dioxo-13-propyl-9-oxa-1-azabicyclo[9.1.1]tridec-4-ene-2-carboxylate (24): The cyclized compound **24** was obtained from the corresponding precursor **23** (550 mg, 1.17 mmol) by using Method B with 2.5 mol-% of Grubbs catalyst at room temp. After 24 h and the usual workup, flash chromatography (CyHex/AcOEt, 1:1) provided the desired β-lactam (350 mg, 67%, yellow oil) as a mixture of stereoisomers. TLC (CyHex/AcOEt, 1:1): R_f = 0.67. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C; major isomer): δ = 8.16 (d, $J_{H,H}$ = 8.2 Hz, 2 H), 7.50 (d, $J_{H,H}$ = 8.2 Hz, 2 H), 5.32–5.54 (m, 2 H), 5.35 (m, 1 H), 5.24 (sharp AB q, 2 H), 3.75 (dd, $J_{H,H}$ = 4.9, $J_{H,H}$ = 10.3 Hz, 1 H), 3.58 (m, 1 H), 2.99 (m, 1 H), 2.77 (dd, $J_{H,H}$ = 1.8, $J_{H,H}$ = 2.0 Hz, 1 H), 2.50 (m, 1 H), 2.43 (m, 2 H), 2.29 (m, 2 H), 1.70 (m, 1 H), 1.44 (m, 1 H), 1.31 (m, 2 H), 1.19 (d, $J_{H,H}$ = 6.4 Hz, 3 H), 0.89 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 171.1, 169.3, 165.8, 147.6, 142.5, 134.0, 128.3, 125.8, 123.6, 65.6, 64.9, 59.7, 57.1, 55.3, 35.0, 34.4, 32.9, 27.0, 19.1, 19.0, 14.0 ppm. HRMS (TOF MS ES+): calcd. for $C_{23}H_{28}N_2O_7$ 467.1794 $[M + Na]^+$; found 467.1807. IR (NaCl): $\tilde{\nu}_{max}$ = 2872–2959, 1751, 1736, 1606, 1522, 1346 cm^{-1}.

(10*R*,11*S*,13*R*)-10-Methyl-8,12-dioxo-13-propyl-9-oxa-1-azabicyclo-[9.1.1]tridecane-2-carboxylic Acid (25): Crude compound **25** was quantitatively obtained as a yellow gum from the cyclized β-lactam **24** (80 mg, 0.18 mmol) by using the procedure described above for the synthesis of compound **3**. TLC (CyHex/AcOEt, 1:1): R_f = 0.65. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C; major stereoisomer): δ = 9.46 (br. s, 1 H), 5.41 (qd, $J_{H,H}$ = 1.7, $J_{H,H}$ = 6.6 Hz, 1 H), 3.70 (ddd, $J_{H,H}$ = 1.7, $J_{H,H}$ = 4.4, $J_{H,H}$ = 9.6 Hz, 1 H), 3.61 (dd, $J_{H,H}$ = 3.2, $J_{H,H}$ = 10.8 Hz, 1 H), 2.83 (dd, $J_{H,H}$ = 1.7, $J_{H,H}$ = 1.7 Hz, 1 H), 2.32 (m, 2 H), 2.27 (m, 1 H), 2.03 (m, 1 H), 1.79 (m, 1 H), 1.35 (m, 2 H), 1.26 (d, $J_{H,H}$ = 6.6 Hz, 3 H), 1.21–1.75 (4 m, 7 H), 0.98 (t, $J_{H,H}$ = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, 25 °C): δ = 173.1, 172.1, 167.9, 65.5, 59.5, 59.3, 56.6, 34.4, 33.8, 27.4, 27.2, 24.6, 23.4, 19.4, 19.0, 14.1 ppm. HRMS (TOF MS ES+): calcd. for $C_{16}H_{25}NO_5$ 334.1630 $[M + Na]^+$; found 334.1618. IR (NaCl): $\tilde{\nu}_{max}$ = 2869–2932, 1747 (br.) cm^{-1}.

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crystallographic structure was resolved by Prof. B. Tinant at UCL. J. M.-B. and G. D. are senior research associates of the FRS-FNRS.

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