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Journal of Organometallic Chemistry 691 (2006) 5406–5422
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Synthesis of 2,3,4,7-tetrahydro-1*H*-azepines as privileged ligand scaffolds for the design of aspartic protease inhibitors via a ring-closing metathesis approach

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Received 3 July 2006; received in revised form 15 September 2006; accepted 15 September 2006
Available online 23 September 2006

Abstract

We have developed a short and highly efficient synthetic strategy towards the hitherto hardly known 3,5- and 3,6-disubstituted 2,3,4,7-tetrahydro-1*H*-azepine scaffold via a ring-closing metathesis approach utilizing inexpensive and readily available starting material such as methyl acrylate and allylamine. Both seven-membered azacycle scaffolds bearing suitable functional groups, which can easily be modified by means of standard synthetic chemistry, serve as non-peptidic heterocyclic core structures for the further design and synthesis of aspartic protease inhibitors. Through specific decoration with appropriate side chains, individual inhibitors can be tailored with respect to selectivity towards particular family members. A first generation of this class of non-peptidic inhibitors have been tested against the aspartic proteases Plasmepsin II and HIV-I protease, respectively, showing promising activity as well as selectivity with IC_{50} values in the micromolar range.

Keywords: Azacycles; RCM; Aspartic proteases; Privileged structures; Azepines

1. Introduction

Throughout the last two decades, ring-closing metathesis (RCM) has become one of the most important tools in organic chemistry and has therefore been reviewed extensively [1]. This elegant approach allows the convenient preparation of a plethora of new molecules and "soon imagination will be the only limit to what molecules can be built" as it was articulated in the press release regarding the award of the Nobel Price in Chemistry 2005 by *The Royal Swedish Academy of Science* [2].

Since RCM has also proven to be a precious tool for the synthesis of five- and six-membered azacycles as well as other nitrogen-containing fused ring systems bearing various substituents [3], we recently engaged in ring-closing metathesis reactions in continuation of our efforts on the synthesis of biologically active nitrogen-containing heterocycles from a medicinal chemist's point of view [4].

At the beginning of the 21st century, Malaria and HIV infections are still among the most serious global health problems causing more than four million deaths per year. Infections by *Plasmodium falciparum*, the most dangerous form of malaria, are responsible or contribute to an estimate of more than two million deaths yearly. Among them, particularly children below an age of five are affected [5]. Infections with the HI-Virus, which inevitably lead to the development of AIDS, claimed the lives of some 2.2 million people alone in sub-Saharan Africa in 2003 [6].

In the patho-physiological processes of both pandemics, aspartic proteases are involved in crucial pathways. During its life cycle, *P. falciparum* degrades the hemoglobin of the host cell to cover its energy and nutrition demands. It has

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doi:10.1016/j.jorganchem.2006.09.031

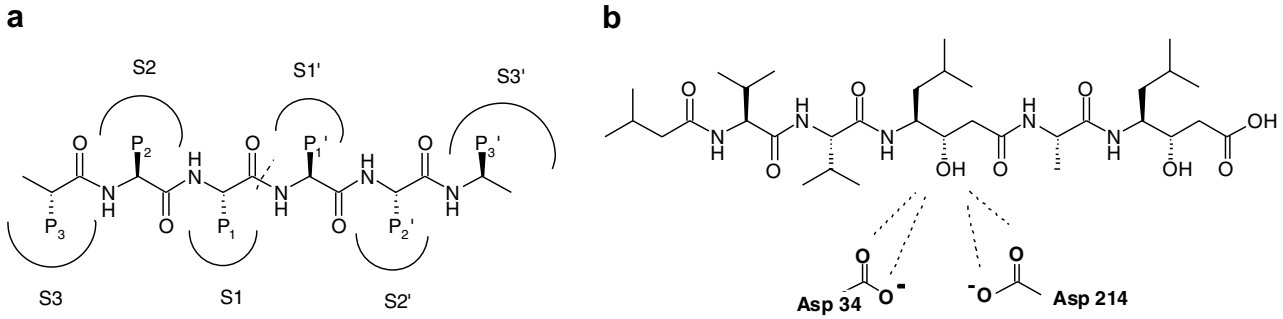


Fig. 1. (a) Nomenclature for substrate residues and their corresponding binding sites. (b) Pepstatine in the active site of Plasmepsin II.

been shown that the inhibition of this metabolic pathway is lethal for the parasite [7]. The aspartic proteases Plasmepsin I, II, and IV, the fundamental hemoglobin degrading enzymes of the parasite, are therefore believed to be attractive targets for the development of an anti-malarial drug therapy [8]. In case of the HI-Virus, HIV protease has proven to be an invaluable drug target due to its essential role in the virus' replication process. However, the continuously increasing resistance towards existing drugs calls for the development of novel anti-infectives favorably possessing a new mechanism of action which is pivotal to combat these afflictions of mankind [9].

Most inhibitors that have been developed so far for the class of aspartic proteases are transition state analogues such as statine and norstatine derivatives addressing via a hydroxyl or hydroxyl-like moiety the two aspartate residues present in the enzyme's active site and thus replacing the native substrate in the peptide's cleavage site as shown in Fig. 1 [10]. The catalytic mechanism of aspartic proteases is virtually the same, however, differences in specificity result from structural evolution of the sub-pockets (e.g. S3–S3′) for substrate side chain binding. In general, aspartic proteases recognize 6–10 amino acids of their polypeptide substrate (e.g. P3–P3′) very specifically.

Recently, substituted secondary amines, in particular substituted pyrrolidines, have proven to be micromolar inhibitors of the HIV-1 protease [11,12]. These results prompted us to investigate in greater detail the suitability of five- as well as seven-membered azacycles as privileged ligand scaffolds designed to address the key interactions of the conserved recognition pattern of the aspartic protease family. In this article, however, we would like to focus primarily on the metal-catalyzed synthesis and biological evaluation of substituted 2,3,4,7-tetrahydro-1*H*-azepines utilizing this seven-membered azacycle scaffold as non-peptidic heterocyclic core structure for the further design and synthesis of selective aspartic protease inhibitors.

2. Results and discussion

2.1. Synthesis

Preliminary modelling studies indicated that the 2,3,4,7-tetrahydro-1*H*-azepine scaffold bearing suitable anchoring groups for the later introduction of various substituents in the positions 3 and 5 and/or 6, respectively, would be the most promising starting point. As depicted in Fig. 2, the azacycle ring system addresses via its basic nitrogen the conserved catalytic dyad. Through specific decoration with appropriate side chains, individual inhibitors can be tailored with respect to selectivity towards particular family members.

The main synthetic challenge associated with this approach of using a privileged ligand scaffold was the development of a synthetic strategy towards an advanced intermediate for each of the azepine core-structures **1**–**3**. They should bear at least two suitable anchoring groups which enable us to introduce a variety of different side chains at a later stage of the synthesis by means of standard synthetic chemistry as outlined in Scheme 1. Furthermore, we envisaged that the convergent syntheses of the desired core structures should preferably comprise the same synthetic intermediates accessible through mainly inexpensive and readily available starting materials. We sought to synthesize our azepine-scaffolds **1**–**3** via an RCM approach. The RCM precursors of type **4** should be obtainable via alkylation of an appropriately functionalized allylamine derivative of type **5** with bromoallyl derivative **6**, each of them readily available through short synthetic sequences commencing with methyl acrylate **7**.

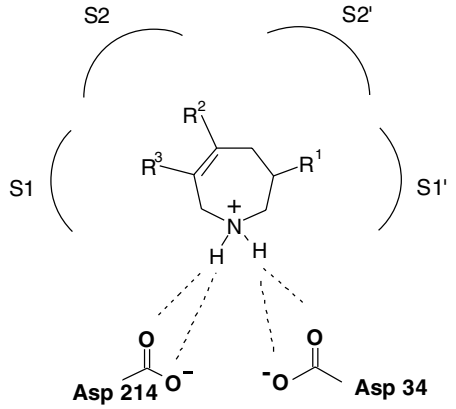
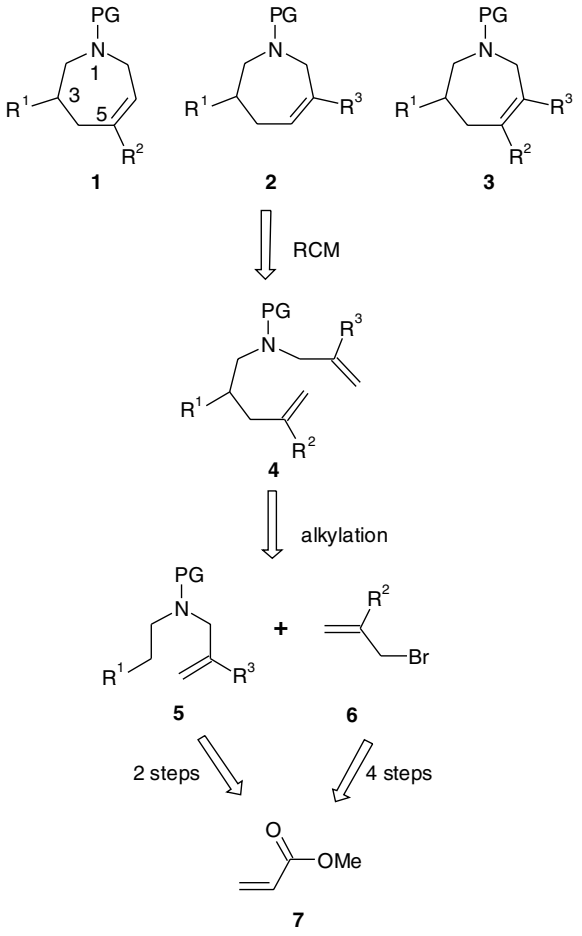


Fig. 2. Putative schematic binding mode of the azepine core structure in the active site of Plasmepsin II.



Scheme 1. Retrosynthetic analysis of the target structures **1**–**3**.

For the key step of our synthetic approach only the commercially available Grubbs catalyst 2nd generation was employed (see Fig. 3).

The *N*-protected 2,3,4,7-tetrahydro-1*H*-azepine scaffold of type **12** bearing two anchoring groups, the methyl ester moiety in position 3 as well as the TBS-protected hydroxymethyl functionality in position 5, could easily be synthesized via a straightforward convergent strategy utilizing inexpensive and readily available starting material such as methyl acrylate **7** and allylamine as depicted in Scheme 2. Baylis–Hillmann reaction of methyl acrylate **7** with formaldehyde afforded the α-hydroxymethylated ester. Conversion of the latter into its TBS-ether followed by subsequent reduction with DIBAL-H gave rise to the TBS-protected allylic alcohol, which then was transferred into the corresponding bromide **9**. Addition of allylamine to methyl acrylate **7** and subsequent protection of the amine functionality led to the corresponding β-amino ester **10** in excellent yield. α-Substitution of ester **10** with bromo allyl derivative **9** to form the RCM-precursor **11** turned out to be a crucial step in this reaction sequence. Nevertheless,

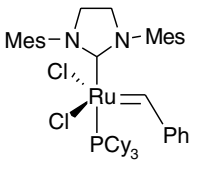
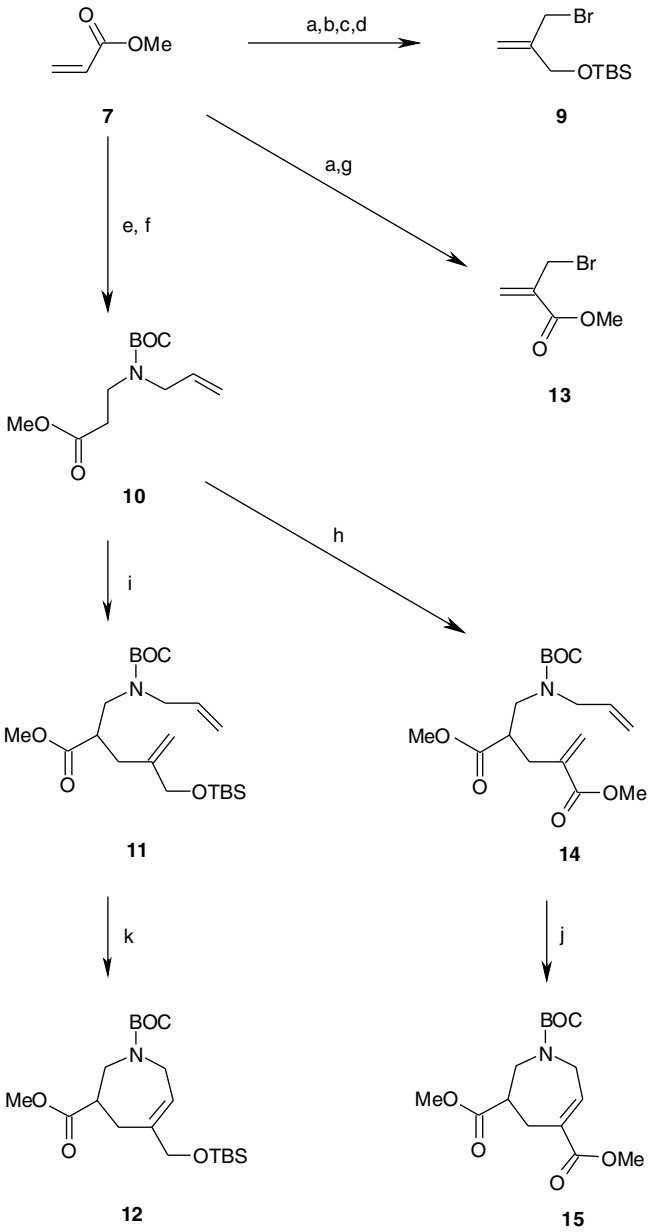


Fig. 3. Grubbs catalyst 2nd generation (**8**).



Scheme 2. Synthesis of **12** and **15**. Reagents and conditions: (a) H_2CO, DABCO, dioxane/H_2O, 15 h, rt, 68%; (b) TBSCl, TEA, DMAP, DCM, 0 °C to rt, 15 h, 91%; (c) DIBAL-H, THF, −78 to 0 °C, 2 h, 80%; (d) TPP/Br_2, imidazole, DCM, 0 °C, 30 min, 84%; (e) allylamine, MeOH, 40 °C, 4 h, 75%; (f) $(BOC)_2O$, TEA, cat. DMAP, DCM, rt, 14 h, 93%; (g) TPP/Br_2, imidazole, DCM, 0 °C, 20 min, 68%; (h) **13**, LDA, DMPU, THF, −40 °C, 4 h, 50%; (i) **9**, LDA, HMPA, THF, −40 °C, 5 h, 84%; (j) Grubbs 2nd generation catalyst 5 mol%, DCM, 40 °C, 8 h, 78%; (k) Grubbs 2nd generation catalyst 5 mol%, DCM, 40 °C, 5 h, 87% [4].

the use of HMPA or DMPU as carbanion-stabilizing additive and freshly prepared LDA furnished the desired α-substituted β-amino ester **11** in good yield. Although the usage of HMPA in general proceeds with slightly higher yields, we mainly used the far less toxic DMPU as additive particularly for large scale preparations. Subjecting this diene **11** to Grubbs 2nd generation catalyst **8** readily rendered the corresponding substituted azepine core structure **12** via a six step procedure in an overall yield of 30% as reported previously [4].

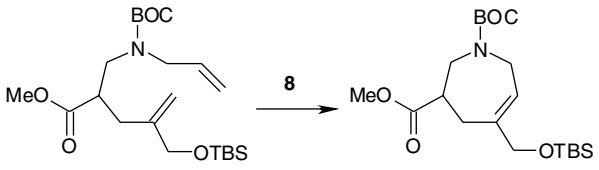
The corresponding *N*-protected 2,3,4,7-tetrahydro-1*H*-azepine **15** featuring two methyl ester functionalities in position 3 and 5 was accessible by means of a similar reaction sequence as shown in Scheme 2. The bromo allyl precursor **13**, which is also commercially available, was synthesized via a two step sequence again employing a Baylis–Hillmann reaction in the first step. The resulting α-hydroxymethylated ester was then converted into bromo derivative **13** [13]. Subsequent reaction with β-amino ester **10** applying the above reaction conditions gave rise to diene **14** which was analogously subjected to Grubbs 2nd generation catalyst yielding **15** in moderate overall yield.

Having developed a straightforward and high yielding synthetic route towards the 3,5-disubstituted *N*-protected 2,3,4,7-tetrahydro-1*H*-azepines of type **12** and **15**, respectively, we next concentrated on the reduction of the Grubbs catalyst load, as it is known that incomplete removal of the catalyst may not only cause side reactions or even decomposition of the reaction products, but, if not removed by the final stage of the synthesis, could influence the outcome of the biological evaluation. Moreover, ruthenium species are also considered as potentially toxic [14]. Furthermore, it was of utmost importance to us to run this key reaction step on a multi-gram scale as the RCM reaction turned out to be the bottleneck in our synthetic sequence. Usually, RCM reactions are run in high dilution to minimize formation of dimeric alkene side products arising from, e.g. cross-metathesis reactions [15]. In contrast, we not only intended to reduce the catalyst load but also to run the reaction in a more concentrated fashion. Therefore, we subjected diene **11** to Grubbs 2nd generation catalyst **8** under standardized conditions concerning reaction time, reaction temperature as well as workup procedure (DCM, reflux, 8 h).

The reaction was still found to proceed smoothly when the amount of the catalyst was decreased from 5 mol% (Table 1, entry 1) to 2.5 mol% (Table 1, entry 2). In both cases the product was obtained in equally high yields after column chromatography. In a next run (Table 1, entry 3) we kept the amount of catalyst at 2.5 mol%, but now the volume of solvent was halved resulting in about the same concentration of catalyst as compared to the original reaction conditions (Table 1, entry 1). As we did not notice any significant change regarding the product yield obtained in the reaction, we investigated to what extend the amount of catalyst could be lowered while keeping the overall concentration of the catalyst constant (Table 1, entries 4 and 5). Even with 0.5 mol% of Grubbs catalyst the reaction progressed equally well.

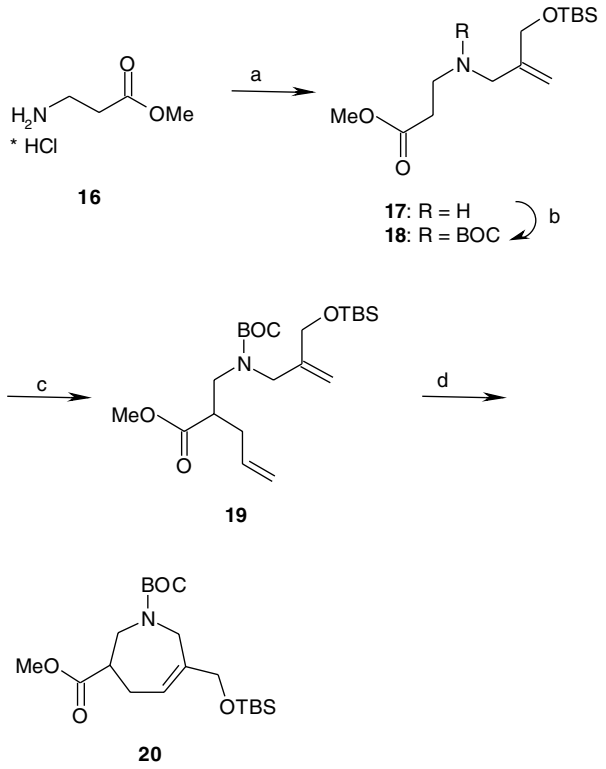
For the synthesis of the 3,6-disubstituted *N*-protected azepines of type **20** we sought to alter our synthetic sequence as little as possible but rather rely on our hitherto developed synthetic procedures for the 3,5-disubstituted derivatives of type **12** according to Scheme 3. Alkylation of β-alanine methyl ester hydrochloride **16** with allylic precursor **9** followed by protection of the resulting secondary amine with di-*tert*-butyl-dicarbonate gave rise to the *N*-BOC-protected β-amino ester **18** in moderate overall yield. However, attempts to increase the rather poor yield of the alkylation step by varying the reaction conditions have up to now been to no avail. In a different approach to generate allylamino ester **17** via a reductive amination of **16** with aldehyde **21**, easily generated in good yield starting from methyl acrylate **7** (Scheme 4) [16], remained likewise fruitless. As **16** is commercially available at low price and precursor **9** can easily be prepared in large scale, we therefore decided to keep to our initial reaction step. Substitution of **18** with allyl bromide smoothly rendered diene **19**, which, after being subjected to Grubbs 2nd generation catalyst **8** employing the above-mentioned reaction conditions, furnished the corresponding azepine **20** in a reasonable overall yield.

Table 1
Ring-closing metathesis of **11**

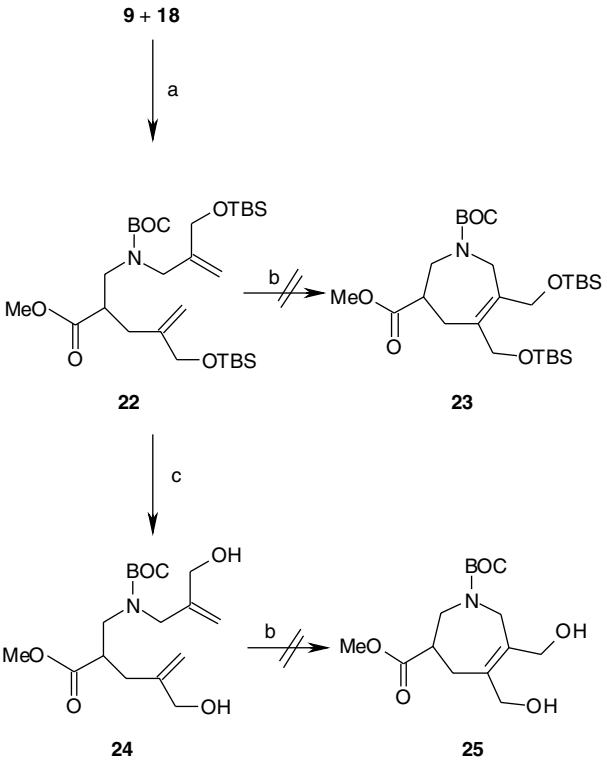


11 **12**

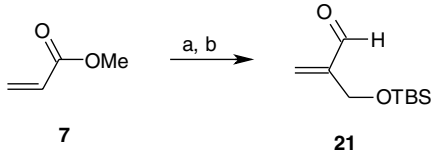
Entry	Amount of **8** (mol%)	Concentration of **11** (mM)	Concentration of **8** (μM)	Yield (%)
1	5	11.8	588	87
2	2.5	11.8	294	81
3	2.5	25	625	90
4	1	50	500	85
5	0.5	100	500	78



Scheme 3. Synthesis of **20**. Reagents and conditions: (a) **9**, TEA, DCM, rt, 16 h, 42%; (b) $(BOC)_2O$, TEA, DMAP, DCM, rt, 12 h, 86%; (c) allyl bromide, LDA, HMPA, THF, −40 °C, 3 h, 81%; (d) Grubbs 2nd generation 1 mol%, DCM, 40 °C, 6.5 h, 82%.



Scheme 5. Attempts to synthesize 3,5,6-trisubstituted azepines **23** and **25**. Reagents and conditions: (a) LDA, HMPA, THF, −40 °C, 4 h, 52%; (b) Grubbs 2nd generation 5 mol%, DCM, 40 °C, 8 h, 0%; (c) HCl in THF, rt, 25 min, 80%.

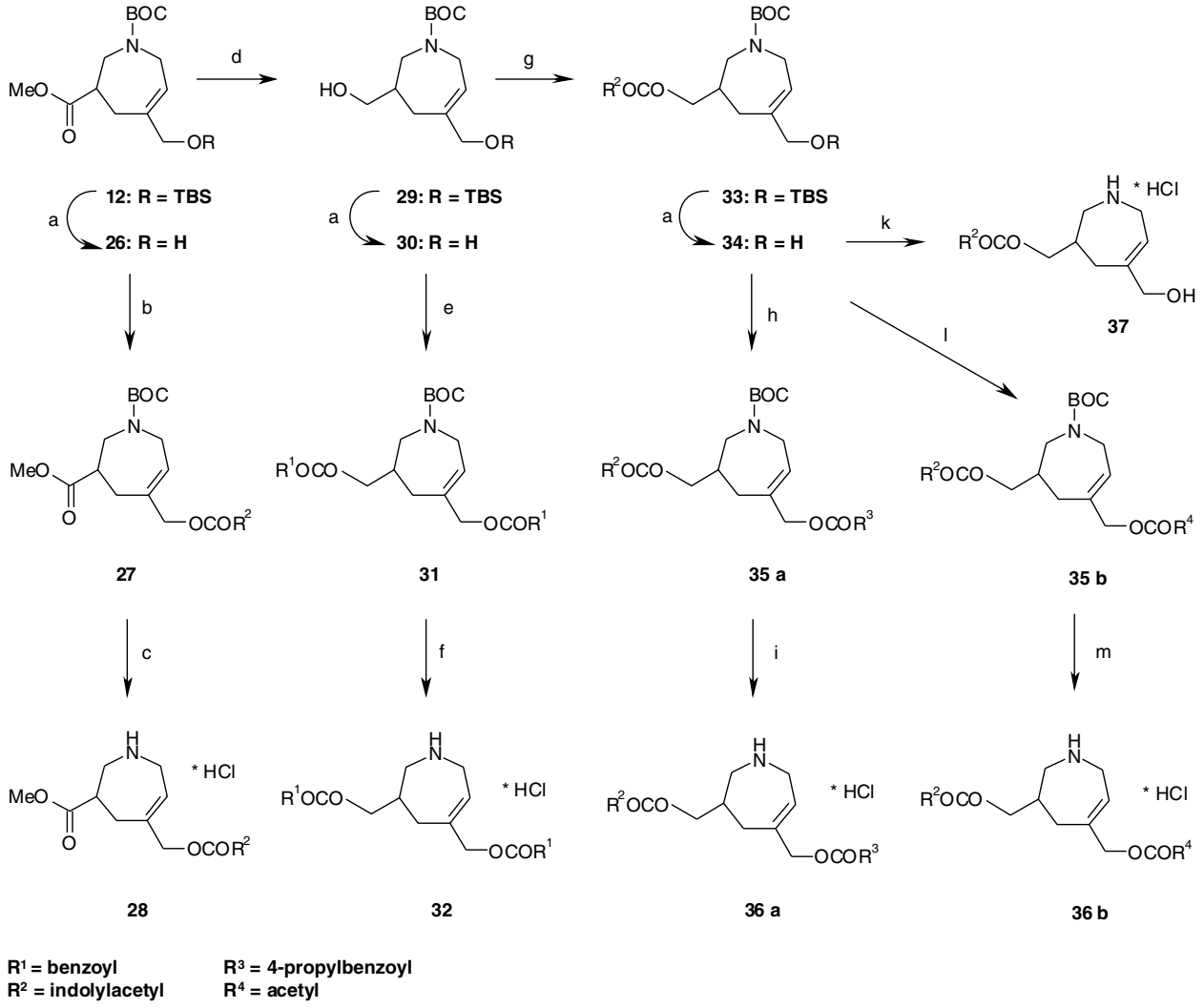


Scheme 4. Synthesis of aldehyde **21** [16]. Reagents and conditions: (a) (i) H_2CO, DABCO, dioxane/H_2O, 15 h, rt, 68%; (ii) TBSCl, TEA, DMAP, DCM, 0 °C to rt, 15 h, 91%; (iii) DIBAL-H, THF, −78 to 0 °C, 2 h, 80%; (b) DMSO, $(COCl)_2$, DIPEA, −78 °C to rt, 1.5 h, 82%.

With a reasonable route to the *N*-BOC-protected β-amino ester **18** in hand, our next challenge was the synthesis of 3,5,6-trisubstituted 2,3,4,7-tetrahydro-1*H*-azepines of type **3**, generating a tetrasubstituted double bond upon ring closure. The formation of tetrasubstituted double bonds via RCM employing Grubbs 2nd generation catalyst is already documented in the literature, however, the outcome seems to be strongly depended on the nature of the utilized diene [17]. In our case, the required precursor **22** is readily available using our previously developed standard protocol via α-substitution of **18** with bromo allyl derivative **9** as depicted in Scheme 5. However, subjecting diene **22** to Grubbs 2nd generation catalyst did not result in formation of **23**, which is probably not surprising in light of the sterically demanding TBS groups. The selective cleavage of both TBS groups proceeded smoothly to form the desired sterically less demanding bis-hydroxymethylated precursor **24**, but to our disappointment we even now did not notice any transformation of **24** into **25** in the following RCM using 5 mol% of Grubbs 2nd generation catalyst in DCM at 40 °C for 8 h. Further studies modifying the reaction conditions as well as employing other commercially available catalysts are currently ongoing.

Having conceived straightforward convergent synthetic strategies towards the class of 3,5-disubsituted and 3,6-disubstituted 2,3,4,7-tetrahydro-1*H*-azepines, respectively, we then focussed on the validation of our concept of using a privileged ligand scaffold for the design and synthesis of selective aspartic protease inhibitors. Both non-peptidic azepine core structures (**12** and **20**) are fitted with suitable functional groups that can easily be modified by means of standard synthetic chemistry thus allowing specific side chain decoration as outlined in Schemes 6 and 7.

Initial modelling studies suggested different carboxylic ester moieties such as acetyl, benzoyl, or indolylacetyl for the side chain decoration of the azepine core structures **26**, **30**, **34**, and **38** in order to induce favourable protein interactions. Selective cleavage of the TBS group in **12** furnishes the corresponding hydroxy methyl derivative **26**, esterification of which with suitable carboxylic acids under standard coupling conditions followed by cleavage of the BOC-protecting group under non-aqueous conditions gives

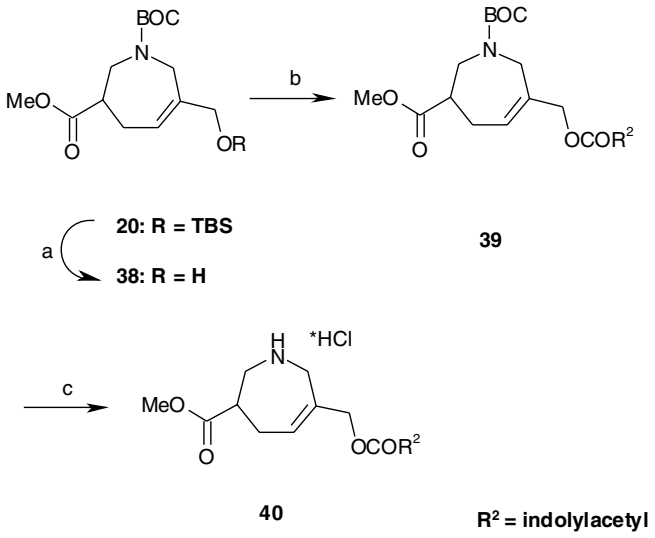


Scheme 6. Reaction pathway towards 3,5-disubstituted inhibitors of type **28**, **32**, **36**, and **37**, respectively. Reagents and conditions: (a) HCl in THF, rt, for **26**: 30 min, 87%, for **30**: 20 min, 87%, for **34**: 40 min, 85%; (b) indole-3-acetic acid, THF/DCM, DIC, DMAP, 14 h, 87%; (c) HCl in diethyl ether, rt, 1.5 h, 89%; (d) DIBAL-H, THF, −78 to 0 °C, 3 h, 76%; (e) benzoyl chloride, TEA, DMAP, DCM, 0 °C to rt, 14 h, 75%; (f) HCl in diethyl ether, rt, 16 h, 75%; (g) indole-3-acetic acid, THF/DCM, DIC, DMAP, 14 h, 82%; (h) 4-propyl-benzoyl chloride, DCM, DIPEA, DMAP, rt, 14 h, 61%; (l) acetyl chloride, DCM, TEA, DMAP, rt, 4 h, 79%; (i) HCl in diethyl ether, rt, 3 h, 92%; (m) HCl in diethyl ether, rt, 8 h, 66%; (k) HCl in diethyl ether, rt, 1.5 h, 93%.

rise to the 3-methoxy-carbonyl azepines **28** as their hydrochloride salts being the first inhibitor type. Reduction of methylester **12** with DIBAL-H to form **29** followed by cleavage of the TBS group renders the bis-hydroxymethylated azepine **30**, which, after bis-esterification and BOC-deprotection, yields the second inhibitor type **32**. The introduction of two divergent side chains aimed to appropriately address the differences in the enzymes' specificity pockets is easily accomplished via the following synthetic pathway: Esterification of the unprotected hydroxyl group in **29** gives rise to **33**, which, after selective deprotection of the TBS group, renders **34**. Further esterification of **34** leads to diester **35**, which upon final cleavage of the BOC-protecting group gives rise to inhibitors of type **36**. Inhibitor core structure **37**, which in contrast to the diesters **28**, **32**, and **36** bears only one ester-functionality as well as a modifiable hydroxymethyl substituent at position 5 is easily accessible from azepines **33** by complete deprotection.

The corresponding 3,6-disubstituted azepines of type **40** are likewise easily accessible following the above synthetic procedure: Cleavage of the TBS group to **38**, followed by esterification to **39** and final deprotection of the BOC-group straightforwardly renders the azepine inhibitors of type **40**. Further functionalizations of this inhibitor type at the methyl ester moiety are currently ongoing.

For synthetic accessibility reasons we considered ester formation. However, we are aware of the fact that for metabolic stability in the further development the ester bonds have to be replaced by some more stable structural elements. This hitherto outlined synthetic approach not only allows the generation of various esters as just described, but, starting from appropriate azepines with unprotected hydroxyl substituents via Swern-oxidation followed by reductive amination, also the preparation of a variety of substituted amines, the synthesis of which will be reported in due course.



Scheme 7. Synthesis of 3,6-disubstituted inhibitor type **40**. Reagents and conditions: (a) HCl in THF, rt, 40 min, 80%; (b) indole-3-acetic acid, DCC, DMAP, THF/DCM, 16 h, 96%; (c) HCl in diethyl ether, 3 h, 92%.

2.2. Biological evaluation

We now directed our efforts on the synthesis of a first series of inhibitors of types **28**, **32**, **36**, **37**, and **40**, respectively, following the above reaction schemes. In case of HIV-I protease, inhibition constants were determined using a competitive binding assay, wherein the initial rate of enzymatic cleavage of the fluorogenic substrate Abz-Thr-Ile-*p*-nitrophenylalanine-Phe-Gln-Arg-NH_2 was measured in presence of varying concentrations of the inhibitors [18]. Analogously, inhibitory constants for Plasmepsin II were determined using Haemoglobin labelled with the fluorogen 7-amino-4-methylcoumarin-3-acetic acid (AMCA) as substrate [19]. IC_{50}-values for selected inhibitors are given in Table 2.

Out of a small set of initially designed and synthesized inhibitors aimed to selectively address Plasmepsin II, compounds decorated with a 1*H*-indolyl-3-acetic acid moiety turned out to be the most active inhibitors (**28**, **36b**, **37**, and **40**) showing promising activity as well as selectivity with IC_{50} values in the micromolar range against Plasmepsin II and HIV-I protease, respectively. Intriguingly, as these inhibitors are just decorated with one larger substituent and therefore only capable to address one of the specificity pockets of the enzyme's active site together with the fact that all inhibitors are racemic mixtures, the obtained IC_{50} values are most promising. Introduction of an acetyl moiety at the hydroxymethyl function in position 5 (**37** versus **36b**) for instance results in a 1.5-fold decrease in potency against Plasmepsin II. Through implementation of a 4-propyl-benzoate moiety instead of the acetyl-substituent in **36**, the specificity can easily be shifted towards HIV-I protease with a 32-fold selectivity against Plasmepsin II (**36a** versus **36b**).

As the most active inhibitors out of our first series all possess a 1*H*-indolyl-3-acetic acid moiety, we wanted to assess whether the inhibitory effect is not only attributed to this moiety. As reported in the literature, medium sized aromatic or aliphatic residues are suitable moieties to address the S1/S1′-pocket of HIV-I protease [10a]. We thus introduced two benzoate moieties in positions 3 and 5 of our azepine core structure giving rise to **32**, which exhibited inhibitory activity and selectivity in a comparable range within this series against HIV-I protease. These results clearly indicate that the 3,5- as well as 3,6-disubstituted 2,3,4,7-tetrahydro-1*H*-azepines are suitable scaffolds for the design and synthesis of selective aspartic protease inhibitors, whereupon individual family members can be addressed through specific decoration with appropriate side chains. First structure–activity relationships derived from these results indicate the necessity to introduce further substituents addressing additional sub-pockets of the enzymes' active sites to increase binding affinity, a project currently ongoing in our group.

3. Conclusion

In summary, we have developed an efficient synthetic route towards 3,5- as well as 3,6-disubstituted azepines via a ring-closing metathesis approach mainly utilizing inexpensive and readily available starting materials. These azepines have been proven to be suitable core structures for the further design and synthesis of aspartic protease inhibitors. Through implementation of appropriate side chains in a first series of inhibitors, we could demonstrate that single family members of the aspartic protease family can be addressed specifically. Our inhibitor scaffolds bear suitable functional groups for further structural modifications by means of standard synthetic procedures giving rise to a variety of second generation inhibitors and thus enables us to probe structure–activity relationships in more detail.

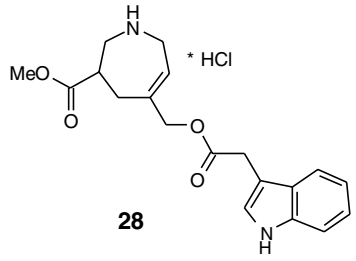
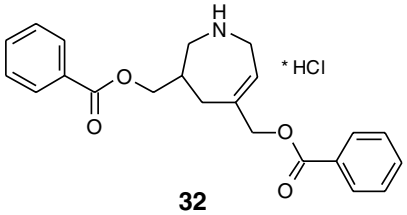
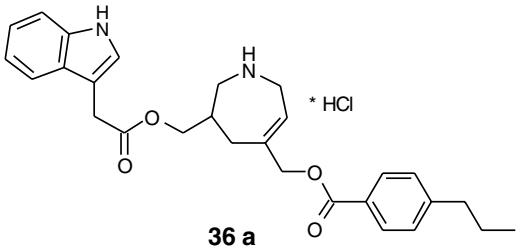
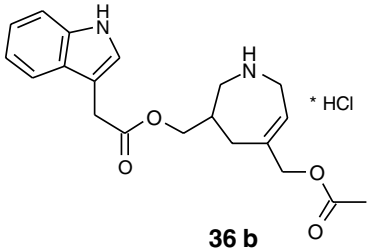
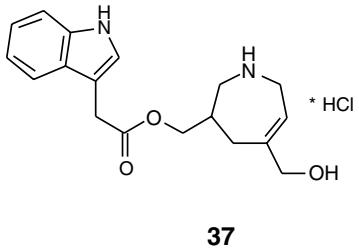
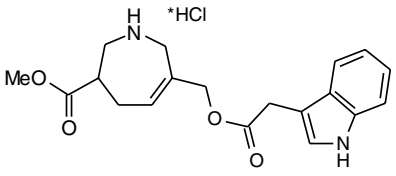
4. Experimental

4.1. Kinetic assays

4.1.1. Determination of inhibition constants toward Plasmepsin II

Plasmepsin II activity assays were performed in 96-well microtiter plates with a Tecan Spectra Fluor spectrometer at excitation wavelength 360 nm and emission wavelength 465 nm. Haemoglobin labelled with the fluorogen 7-amino-4-methylcoumarin-3-acetic acid (AMCA) was used as substrate. For IC_{50} determinations, inhibitors were allowed to equilibrate with enzyme at 37 °C for 5 min. The final substrate concentration was 2.6 μM. The Plasmepsin II concentration, measured by UV/Vis, was 13 nM in an acetate/formate buffer (0.06 M, pH 4.65). DMSO (2.5%) was used to guarantee complete dissolution of the inhibitors. IC_{50} values were taken from plots of v_i/v_0 as a function of inhibitor concentration, for which v_i and v_0 are the initial rates of reaction in presence and absence of

Table 2
IC_{50} values of inhibitors based on the azepine scaffold against HIV-I protease and Plasmepsin II, respectively

Compound	IC_{50} (μM)	
	Plasmepsin II	HIV-I-protease
 **28**	40	~1000
 **32**	>300	72
 **36 a**	>1250	40
 **36 b**	170	>1000
 **37**	125	>1000
 **40**	125	~500

the inhibitor, respectively. Substrate hydrolysis was recorded as an increase in fluorescence intensity over a period of 3 min, during which the intensity increased linearly with time [19].

4.1.2. Determination of inhibition constants toward HIV-I protease

IC_{50} values were taken from plots of v_i/v_0 as a function of inhibitor concentration, for which v_i and v_0 are the catalytic rates in presence and absence of the inhibitor, respectively. The fluorogenic substrate Abz-Thr-Ile-*para*-nitrophenylalanine-Phe-Gln-Arg-NH_2 was purchased from Bachem. Recombinant HIV-I protease was expressed from *Escherichia coli* and purified as previously described [18a]. Enzymatic assays were performed in 172 μl of assay buffer (100 mM MES, 300 mM KCl, 5 mM EDTA, 1 mg/mL BSA, pH 5.5) by adding substrate dissolved in 4 μl DMSO; distinct inhibitor concentrations dissolved in 4 μl DMSO, and 20 μl HIV-I protease solution to give a final volume of 200 μl (final DMSO concentration 4%). The final enzyme concentration was 6.25 nM and the substrate concentration was 20 μM. The hydrolysis of the substrate was recorded as an increase in fluorescence intensity (excitation wavelength 337 nm, emission wavelength 410 nm) over a period of 10 min during which the rate increased linearly with time [18b].

4.2. General synthetic

Reported yields refer to the analytically pure product obtained by distillation or column chromatography. All proton and carbon nuclear magnetic resonance spectra were recorded on a Jeol Eclipse +500 MHz spectrometer (^{1}H NMR: 500 MHz, ^{13}C NMR: 125 MHz). Chemical shifts are stated in parts per million (ppm) and were referenced to TMS at 0.00 ppm (^{1}H) except for compounds containing a silyl protecting group which were referenced to the residual $CHCl_3$ in $CDCl_3$ at 7.24 ppm and to $CDCl_3$ at 77.0 ppm (^{13}C), respectively. NMR spectra were recorded in $CDCl_3$ unless otherwise indicated. Abbreviations: bdd = broad doublet of doublets, bm = broad multiplet, bs = broad singlet, d = doublet, m = multiplet, sm = symmetric multiplet, q = quartet, s = singlet, t = triplet, ps = pseudo. Mass spectra were obtained from a double focussing sectorfield spectrometer typ 7070 H by Vacuum Generators or by a double focussing sectorfield spectrometer typ VG-AutoSpec by Micromass. Combustion analyses were determined on a CH analyzer by Labormatic/Woesthoff or a CHN autoanalyzer 185 (only nitrogen) by Hewlett–Packard. Flash column chromatography was performed using silica gel 60 (0.05–0.1 mm) or silica gel 60 (0.04–0.063 mm) purchased from Macherey-Nagel. TLC was carried out using 0.2 mm aluminium plates coated with silica gel 60 F_{254} by Merck and the products were visualized by UV detection, iodine or by utilization of phosphormolybdic acid (“blue stain”). Solvents and reagents that are commercially available were used without further purification unless otherwise noted. Tetrahydrofuran was dried by distillation from sodium/benzophenone. All moisture-sensitive reactions were carried out using oven-dried glassware under a positive stream of argon. If necessary, solvents were deoxygenated by standard procedures. Grubbs’ 2 was purchased from Sigma–Aldrich.

Compounds **9**, **10**, **11**, **12** and **26** have been prepared according to the literature.

4.2.1. 5-(tert-Butyl-dimethyl-silanyloxymethyl)-2,3,4,7-tetrahydro-1H-azepine-1,3-dicarboxylic acid-1-tert-butyl ester 3-methyl ester (*12*)

The title compound has been prepared according to a modified literature procedure [4].

A solution of **11** in 190 mL of thoroughly degassed DCM was heated to 40 °C and benzyliden-[1,3,-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro-(tricyclohexylphosphine)-ruthenium **8** (Grubbs 2 catalyst, 1 mol%), dissolved in 10 mL of degassed DCM, was added to the reaction mixture. After stirring for 8 h at 40 °C, the reaction mixture was allowed to reach room temperature. After quenching the reaction through addition of 20 mL of DMSO [20] and subsequent stirring for 12 h, the reaction mixture was washed three times with diluted NaCl-solution, twice with brine, dried over $MgSO_4$, and filtered. Removal of the solvent under reduced pressure followed by column chromatography (hexane/*t*-BuOMe: 8:1) of the oily residue gave rise to 3.584 g (83%) of **12**. The isolated product exhibited identical spectroscopic data to those reported previously.

4.2.2. 2-Bromomethyl-acrylic acid methyl ester (*13*) [13]

To a solution of triphenylphoshine (TPP, 5.120 g, 19.53 mmol, 1.1 equiv.) in DCM (30 mL), a solution of bromine (1 mL, 19.52 mmol, 1.1 equiv.) in 10 mL of DCM was added dropwise at 0 °C. The reaction mixture was stirred until a colourless precipitate indicated the formation of the desired phosphonium salt, which was then added slowly to a solution of imidazole (1.450 g, 21.30 mmol, 1.2 equiv.) and 2-hydroxymethyl-acrylic acid methyl ester [4] (2.060 g, 17.75 mmol, 1.0 equiv.) in 30 mL DCM at 0 °C. After stirring for 20 min maintaining the temperature at 0 °C, the reaction mixture was poured into an ice–water mixture and extracted twice with *t*-BuOMe. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual slurry was re-dissolved in a small amount of DCM and added dropwise into hexane giving rise to a suspension, which was filtered, and washed thoroughly. After concentration of the filtrate under vacuum, hexane was added to the residual suspension, which was filtered again and concentrated under reduced pressure. Bulb to bulb distillation (40 °C/2.2×10^{-2} mbar) of the remaining residue afforded 2.152 g (68%) of **13** as a colourless oil: ^{1}H NMR δ 6.34 (s, 1H), 5.97 (s, 1H), 4.19 (s, 2H), 3.82 (s, 3H); ^{13}C NMR δ 165.2, 137.2, 129.1, 52.2,

29.2; MS (EI) *m/z* 180 (53, $M^+[Br^{81}]$), 178 (54, $M^+[Br^{79}]$), 149 (30), 147 (33), 121 (29), 119 (18), 99 (100).

4.2.3. 2-[(Allyl-tert-butoxycarbonyl-amino)-methyl]-4-methylene-pentane dioic acid dimethyl ester (**14**)

To a solution of *n*-BuLi (2.5 M in hexane, 1.6 mL, 4.0 mmol, 2.0 equiv.) in THF, neat diisopropyl amine (0.56 mL, 4.0 mmol, 2.0 equiv.) was added at −78 °C. The reaction was allowed to reach 0 °C, stirred for additional 10 min, and cooled again to −78 °C. A solution of β-amino ester **10** [4] (0.972 g, 4.0 mmol, 2.0 equiv.) dissolved in THF was added slowly. After stirring for 30 min, 4 mL of DMPU were added, followed by the addition of a solution of allyl bromide derivative **13** (0.328 g, 2.0 mmol, 1.0 equiv.) in THF. The reaction mixture was warmed to −40 °C and kept at this temperature until TLC indicated completion of the reaction (≈4 h). After subsequent addition of diethyl ether and a saturated NH_4Cl-solution, the organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The remaining product was purified by flash chromatography (hexane/*t*-BuOMe: 4:1) and gave rise to 0.341 g (50%) of **14** as colourless oil: ^{1}H NMR δ (rotamers, ratio: ∼1:1) 6.19 (d, 1H, $J = 1.2$ Hz), 5.80–5.70 (sm, 1H), 5.61 (psd, 1H, $J = 18.3$ Hz), 5.12 (bs, 2H), 3.98 (d, 0.5H, $J = 14.9$ Hz), 3.88–3.80 (m, 0.5H), 3.73 (s, 3H), 3.73–3.67 (m, 1H), 3.64 (s, 3H), 3.43–3.30 (bm, 2H), 3.08–3.02 (sm, 1H), 2.63–2.45 (bm, 2H), 1.47 (s, 4.5H), 1.44 (s, 4.5H); ^{13}C NMR δ (rotamers) 174.4, 166.9, 166.8, 155.4, 155.2, 137.2, 133.8, 133.7, 127.1, 116.6, 116.1, 80.0, 79.7, 51.9, 51.6, 50.4, 49.8, 48.6, 44.0, 43.6, 32.8, 32.3, 28.3; MS (ES+) *m/z* 364 (100, $[M+Na]^+$), 705 (23, $[2M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{17}H_{28}NO_6$: 342.191663; found: 342.191758.

4.2.4. 2,3,4,7-Tetrahydro-azepine-1,3,5-tricarboxylic acid 1-tert-butyl ester 3,5-dimethyl ester (**15**)

A solution of **14** (0.341 g, 1.0 mmol, 1.0 equiv.) in 90 mL of thoroughly degassed DCM was heated to 40 °C and benzyliden-[1,3,-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro-(tricyclohexylphosphine)-ruthenium (0.043 g, 0.05 mmol, 5 mol%, Grubbs 2 catalyst), dissolved in 5 mL of degassed DCM, was added to the reaction mixture. After stirring for 8 h at 40 °C, the reaction mixture was allowed to reach room temperature and stirred for 12 h at ambient temperature. The reaction mixture was concentrated under reduced pressure followed by column chromatography (hexane/*t*-BuOMe: 2:1) of the oily residue which gave rise to 0.244 g (78%) of **15** as colourless oil: ^{1}H NMR (rotamers, ratio: ∼1.4:1) δ 6.92 (s, 1H), 4.33 (d, 0.60H, $J = 16.7$ Hz), 4.27 (d, 0.43H, $J = 18.6$ Hz), 4.13 (dd, 0.59H, $J = 17.2$, 3.9 Hz), 4.00 (dd, 0.43H, $J = 18.3$, 3.6 Hz), 3.93 (dd, 0.45H, $J = 14.0$, 6.4 Hz), 3.80–3.77 (m, 0.40 Hz), 3.77 (s, 1.33H), 3.75 (s, 1.68H), 3.71 (s, 1.70H), 3.69 (s, 1.29H), 3.69–3.60 (m, 1H), 3.05–2.94 (m, 1H), 2.88–2.78 (m, 2H), 1.47 (s, 5.39H), 1.46 (s, 3.97H); ^{13}C NMR (rotamers) δ 173.5, 167.3, 155.0, 139.2, 139.1, 131.6, 130.5, 80.3, 80.2, 52.0, 51.8, 47.5, 47.2, 47.1, 42.6, 42.2, 28.2, 25.7, 25.0; MS (ES+) *m/z* 336 (100, $[M+Na]^+$), 649 (86, $[2M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{15}H_{23}NO_6Na$: 336.142307; found: 336.140934.

4.2.5. 3-[2-(tert-Butyl-dimethyl-silanyloxymethyl)-allylamino]-propionic acid methyl ester (**17**)

To a stirred suspension of β-alanin methyl ester hydrochloride (0.698 g, 5.00 mmol, 1.0 equiv.) in DCM (50 mL), TEA (1.48 mL, 10.50 mmol, 2.1 equiv.) was added followed by the dropwise addition of (2-Bromomethyl-allyloxy)-*tert*-butyl-dimethylsilane **9** [4] (1.390 g, 5.25 mmol, 1.05 equiv.) in DCM (10 mL) at 0 °C. The reaction mixture was stirred at this temperature for 30 min, warmed to ambient temperature and stirred for an additional 16 h. After subsequent addition of diethyl ether and saturated NH_4Cl-solution, the organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (hexane/ethyl acetate: 1:1) gave rise to 0.595 g (42%) of **17** as colourless oil: ^{1}H NMR δ 5.09 (s, 1H), 4.97 (s, 1H), 4.13 (s, 2H), 3.66 (s, 3H), 3.23 (s, 2H), 2.83 (t, 2H, $J = 6.4$ Hz), 2.49 (t, 2H, $J = 6.4$ Hz), 1.58 (bs, 1H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 173.0, 146.5, 110.2, 64.8, 51.6, 51.3, 44.2, 34.4, 25.8, 18.2, −5.5; MS (ES+) *m/z* 288 (100, $[M+H]^+$); HRMS (ES+) *m/z* calcd for $C_{14}H_{30}NO_3Si$: 288.199498; found: 288.200005.

4.2.6. 3-{tert-Butoxycarbonyl-[2-(tert-butyl-dimethyl-silanyloxymethyl)-allyl]-amino}-propionic acid methyl ester (**18**)

To a solution of **17** (1.010 g, 3.50 mmol, 1.0 equiv.), TEA (0.591 mL, 4.20 mmol, 1.2 equiv.) and a catalytic amount of DMAP in DCM at 0 °C, a solution of $(BOC)_2O$ (0.920 g, 4.20 mmol, 1.2 equiv.) in DCM was added dropwise over a period of 30 min. The reaction mixture was allowed to reach room temperature and stirred for an additional 12 h. After subsequent addition of *t*-BuOMe and a saturated NH_4Cl-solution, the organic layer was separated and the aqueous layer was extracted twice with *t*-BuOMe. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (hexane/ethyl acetate: 9:1) gave rise to 1.170 g (86%) of **18** as colourless oil: ^{1}H NMR (rotamers, ratio ∼1:1) δ 5.15 (s, 0.5H), 5.11 (s, 0.5H), 4.88 (s, 0.5H), 4.86 (s, 0.5H), 4.05 (s, 2H), 3.83 (s, 1H), 3.80 (s, 1H), 3.64 (s, 3H), 3.49–3.37 (bs, 2H), 2.60–2.48 (bs, 2H), 1.43 (s, 4.5H), 1.41 (s, 4.5H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (rotamers) δ 172.3, 172.1, 155.3, 144.6, 144.4, 110.6, 110.2, 79.7, 64.0, 63.9, 51.5, 49.9, 49.0, 42.9, 42.6, 33.3, 32.9, 28.2, 25.8, 25.6, 18.2, 14.1, −3.7, −5.5; MS (ES+) *m/z* 410 (100, $[M+Na]^+$), 797 (100, $[2M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{19}H_{37}NO_5SiNa$: 410.233872; found: 410.233324.

4.2.7. 2-({tert-Butoxycarbonyl-2[-(tert-butyl-dimethyl-silanyloxymethyl)-allyl]-amino}-methyl)-pent-4-enoic acid methyl ester (**19**)

To a solution of *n*-BuLi (2.5 M in hexane, 1.84 mL, 4.60 mmol, 1.0 equiv.) in THF (8 mL), neat diisopropyl amine (0.35 mL, 2.50 mmol, 1.0 equiv.) was added at −78 °C. The reaction mixture was allowed to reach 0 °C, stirred for additional 15 min, and cooled again to −78 °C. A solution of **18** (1.800 g, 4.60 mmol, 1.0 equiv.), dissolved in THF, was added slowly. After stirring for 30 min, a solution of allyl bromide (0.840 g, 0.6 mL, 6.90 mmol, 1.5 equiv.) in HMPA (1.2 mL, 6.90 mmol, 1.5 equiv.) was then added slowly. The reaction mixture was warmed to −40 °C and kept at this temperature until TLC indicated the completion of reaction (≈3 h). After subsequent addition of diethyl ether and saturated NH_4Cl-solution, the organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (hexane/*t*-BuOMe: 10:1) afforded 1.590 g (81%) of **19** as colourless oil: ^{1}H NMR (rotamers, ratio: ∼1:1) δ 5.75–5.64 (sm, 1H), 5.14 (bs, 0.5H), 5.12 (bs, 0.5H), 5.04 (dd, 1H, $J = 17.1$, 1.5 Hz), 5.00 (d, 1H, $J = 9.8$ Hz), 4.82 (bs, 1H), 4.02 (s, 2H), 3.94 (d, 0.5H, $J = 15.9$ Hz), 3.85 (d, 0.5H, $J = 16.2$ Hz), 3.68 (d, 1H, $J = 16.2$ Hz), 3.64 (s, 3H), 3.38–3.25 (bs, 2H), 2.90–2.75 (bs, 1H), 2.36–2.25 (sm, 1H), 2.23–2.10 (bs, 1H), 1.43 (s, 4.5H), 1.40 (s, 4.5H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (rotamers) δ 174.6, 155.4, 144.5, 144.2, 134.6, 117.2, 117.0, 110.5, 110.1, 79.9, 79.7, 64.1, 64.0, 51.6, 50.1, 49.2, 48.6, 48.0, 44.6, 44.1, 34.3, 28.3, 28.8, 18.3, −5.5; MS (ES+) *m*/*z* 428 (100, $[M+H]^+$), 878 (43, $[2M+H+Na]^+$); HRMS (ES+) *m*/*z* calcd for $C_{22}H_{42}NO_5Si$: 428.283227; found: 428.285523. Anal. Calc. for $C_{22}H_{41}NO_5Si$: C, 61.79; H, 9.66; N, 3.28. Found: C, 61.88; H, 9.60; N, 3.23%.

4.2.8. 6-(tert-Butyl-dimethyl-silanyloxymethyl)-2,3,4,7-tetrahydro-azepine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester (**20**)

A solution of **19** (1.300 g, 3.00 mmol) in 50 mL thoroughly degassed DCM was heated to 40 °C and benzyliden-[1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro-(tricyclohexyl-phosphine)-ruthenium (Grubbs 2 catalyst, 1 mol%, 25.5 mg, 0.03 mmol), dissolved in 5 mL of degassed DCM, was added to the reaction mixture. After stirring for 6.5 h at 40 °C, the reaction mixture was allowed to reach room temperature. After quenching the reaction through addition of 20 mL of DMSO [20] and stirring for 12 h, the reaction mixture was washed three times with diluted NaCl-solution, twice with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (hexane/*t*-BuOMe: 10:1) of the oily residue gave rise to 0.980 g (82%) of **20** as colourless oil: ^{1}H NMR (rotamers, ratio: ∼1.1:1) δ 5.70–5.64 (sm, 1H), 4.11–4.04 (m, 1.46H), 4.04–3.99 (m, 1.56H), 3.99–3.90 (m, 0.79H), 3.86–3.71 (sm, 1.25H), 3.67 (s, 1.62H), 3.65 (s, 1.42H), 3.52–3.46 (sm, 1H), 2.89–2.79 (m, 1H), 2.51–2.35 (m, 2H), 1.42 (s, 9H), 0.88 (s, 4.7H), 0.87 (s, 4.3H), 0.04 (s, 3.2H), 0.03 (s, 2.8H); ^{13}C NMR (rotamers) δ 173.9, 155.1, 155.0, 140.9, 140.5, 122.3, 121.1, 79.76, 79.72, 66.34, 66.32, 51.7, 48.8, 48.5, 47.9, 47.6, 43.3, 42.8, 28.4, 27.3, 26.3, 25.8, 18.2, −5.4; MS (ES+) *m*/*z* 400 (100, $[M+H]^+$); HRMS (ES+) *m*/*z* calcd for $C_{20}H_{38}NO_5Si$: 400.251927; found: 400.250423.

4.2.9. 2-(tert-Butyl-dimethyl-silanyloxymethyl)-propenal (**21**) [16]

DMSO (2.13 mL, 30.00 mmol, 3.0 equiv.) was added dropwise to a stirred solution of oxalyl chloride (1.29 mL, 15.00 mmol, 1.5 equiv.) in DCM (20 mL) at −78 °C. After stirring for additional 10 min, a solution of 2-hydroxymethyl-acrylic acid methyl ester (2.024 g, 10.00 mmol, 1.0 equiv.) [4] in 20 mL DCM was added slowly. After stirring for 1 h, *N*-ethyl diisopropylamine (10.27 mL, 60.00 mmol, 6.0 equiv.) was added slowly. The reaction mixture was warmed to room temperature and stirred for 10 min. After quenching the reaction through addition of 40 mL H_2O and diluting with DCM, the organic layer was separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed three times with 1 N HCl, three times with saturated $NaHCO_3$-solution, twice with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (hexane/*t*-BuOMe: 100:3) gave rise to 1.640 g (82%) of **21** as colourless oil: ^{1}H NMR δ 9.59 (s, 1H), 6.50 (dd, 1H, $J = 3.2$, 2.1 Hz), 6.08 (dd, 1H, $J = 3.2$, 1.8 Hz), 4.37 (t, 2H, $J = 2.1$ Hz), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR δ 193.4, 149.5, 132.5, 59.5, 25.6, 18.2, −5.6; MS (ES+) *m*/*z* 201 (100, $[M+H]^+$), 231 (28, $[M+MeOH]^+$).

4.2.10. 2-({tert-Butoxycarbonyl-[2-(tert-butyl-dimethyl-silanyloxymethyl)-allyl]-amino}-methyl)-4-(tert-butyl-dimethyl-silanyloxymethyl)-pent-4-enoic acid methyl ester (**22**)

To a solution of *n*-BuLi (2.5 M in hexane, 1.0 mL, 2.50 mmol, 1.06 equiv.) in THF (5 mL), neat diisopropyl amine (0.35 mL, 2.50 mmol, 1.06 equiv.) was added at −78 °C. The reaction mixture was allowed to reach 0 °C, stirred for additional 15 min, and cooled again to −78 °C. A solution of **18** (0.910 g, 2.35 mmol, 1.0 equiv.) dissolved in THF was added slowly. After stirring for 30 min, a solution of bromo allyl derivative **9** (0.660 g, 2.50 mmol, 1.06 equiv.) in HMPA (0.44 mL, 2.50 mmol, 1.06 equiv.) was then added slowly. The reaction mixture was warmed to −40 °C and kept at this temperature until TLC indicated the completion of reaction (≈4 h). After subsequent addition of diethyl ether and saturated NH_4Cl-solution, the organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (hexane/ethyl acetate: 10:1) afforded 0.694 g (52%) of **22** as colourless oil: ^{1}H

NMR δ (rotamers, ratio: ~1:1) 5.15 (bs, 0.5H), 5.10 (bs, 0.5H), 5.04 (s, 1H), 4.82 (s, 2H), 4.03 (s, 4H), 3.95 (d, 0.5H, $J = 16.0$ Hz), 3.84 (d, 0.5H, $J = 16.5$ Hz), 3.67 (d, 1H, $J = 17.2$ Hz), 3.62 (s, 3H), 3.31 pst (2H), 3.03–2.90 (bs, 1H), 2.35–2.20 (m, 1H), 2.16–2.05 (m, 1H), 1.44 (s, 4.5H), 1.40 (s, 4.5H), 0.88 (s, 9H), 0.87 (s, 9H), 0.04 (s, 12H); ^{13}C NMR δ (rotamers) 174.8, 155.4, 145.3, 144.5, 144.2, 110.8, 110.6, 110.2, 80.0, 79.7, 65.6, 64.1, 64.0, 51.7, 50.1, 49.2, 49.0, 48.7, 43.5, 43.0, 33.2, 28.3, 25.9, 18.3, −5.4; MS (ES+) *m/z* 572 (30, $[M+H]^+$), 594 (65, $[M+Na]^+$), 1165 (100, $[2M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{29}H_{57}NO_6NaSi_2$: 594.362216; found: 594.358649.

4.2.11. 2-{[tert-Butoxycarbonyl-(2-hydroxymethyl-allyl)-amino]-methyl}-4-hydroxymethyl-pent-4-enoic acid methyl ester (**24**)

0.516 g (0.90 mmol) of **22** was dissolved in a 30:1 mixture of THF and aqueous HCl 32% and stirred at room temperature for 25 min. After addition of a saturated $NaHCO_3$-solution, the reaction mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (hexane/*t*-BuOMe: 1:3) of the oily residue gave rise to 0.235 g (80%) of **24** as colourless oil: ^{1}H NMR (DMSO-d_6, rotamers) δ 5.05 (s, 1H), 4.98 (s, 1H), 4.82 (pst, 2H), 4.77–4.72 (m, 2H), 3.90–3.78 (m, 5H), 3.70–3.60 (bs, 1H), 3.56 (bs, 3H), 3.28–3.20 (m, 2H), 2.97–2.88 (m, 1H), 2.21 (dd, 1H, $J = 14.7$, 9.2 Hz), 2.07 (dd, 1H, $J = 14.7$, 5.7 Hz), 1.38 (s, 9H); ^{13}C NMR (rotamers) δ 175.0, 174.7, 156.3, 155.5, 145.4, 144.5, 113.4, 112.3, 112.0, 111.3, 80.8, 80.2, 65.2, 63.4, 51.7, 50.2, 49.4, 48.8, 43.4, 43.0, 33.6, 28.1; MS (ES+) *m/z* 366 (100, $[M+Na]^+$), 709 (70, $[2M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{17}H_{29}NO_6Na$: 366.189258; found: 366.187395.

4.2.12. 5-Hydroxymethyl-2,3,4,7-tetrahydro-azepine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester (**26**)

Compound **26** has already been prepared by us via a different route [4].

Compound **12** (1.600 g, 4.00 mmol, 1.0 equiv.) was dissolved in a 30:1 mixture of THF and aqueous HCl 32% and stirred at room temperature for 30 min. After addition of a saturated $NaHCO_3$-solution, the reaction mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. Column chromatography (hexane/*t*-BuOMe: 1:1) of the oily residue afforded 0.987 g (87%) of **26** as a colourless oil, which exhibited identical spectroscopic data to those obtained using the method described earlier [4].

4.2.13. 5-(2-1H-Indol-3-yl-acetoxymethyl)-2,3,4,7-tetrahydro-azepine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester (**27**)

To a stirred solution of indole-3-acetic acid (0.725 g, 4.14 mmol, 1.2 equiv.) in a 1:1 mixture of THF/DCM (15 mL) were added **26** (0.984 g, 3.45 mmol, 1.0 equiv.) dissolved in a 1:1 mixture of THF/DCM and DMAP (0.021 g, 0.17 mmol, 5 mol%) followed by the dropwise addition of a solution of DIC (0.70 mL, 4.49 mmol, 1.3 equiv.) in a 1:1 mixture of THF/DCM. The reaction mixture was stirred at room temperature for 14 h, then carefully quenched by addition of a saturated $NaHCO_3$-solution and the layers were separated. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were washed twice with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was re-dissolved in a small amount of acetone p.a., insoluble material was filtered off, and the resulting residue was thoroughly washed with acetone p.a. The combined acetone layers were concentrated under reduced pressure. Column chromatography of the oily residue (hexane/*t*-BuOMe: 1:1) afforded 1.326 g (87%) of **27** as a colourless oil: ^{1}H NMR δ (rotamers, ratio: ~1.2:1) 8.19 (s, 1H), 7.60 (d, 1H, $J = 7.3$ Hz), 7.35 (d, 1H, $J = 8.3$ Hz), 7.19 (t, 1H, $J = 7.2$ Hz), 7.16 (d, 1H, $J = 2.3$ Hz), 7.12 (pst, 1H, $J = 7.1$ Hz), 5.67 (s, 0.47H), 5.62 (s, 0.56H), 4.49 (s, 2H), 4.14–4.01 (sm, 1H), 3.97–3.84 (sm, 1H), 3.80 (s, 2H), 3.77–3.70 (sm, 1H), 3.69 (s, 1.67H), 3.66 (s, 1.33H), 3.60–3.46 (sm, 1H), 2.80–2.77 (m, 1H), 2.45–2.31 (m, 2H), 1.45 (s, 4.93H), 1.43 (s, 4.09H); ^{13}C NMR δ (rotamers) 173.7, 171.7, 155.3, 155.1, 136.1, 135.0, 133.6, 127.1, 126.8, 126.1, 123.2, 122.0, 119.4, 118.6, 111.2, 108.0, 80.1, 79.9, 69.1, 51.8, 48.0, 47.6, 46.6, 46.4, 42.7, 42.1, 31.3, 28.6, 28.32, 28.25, 27.8; MS (ES+) *m/z* 465 (100, $[M+Na]^+$), 907 (49, $[2M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{24}H_{30}N_2O_6Na$: 465.200157; found: 465.197041.

4.2.14. 5-(2-1H-Indol-3-yl-acetoxymethyl)-3-methoxycarbonyl-2,3,4,7-tetrahydro-1H-azepinium chloride (**28**)

A suspension of **27** (0.100 g, 0.23 mmol, 1.0 equiv.) in a 2 M solution of hydrogen chloride in diethyl ether (2.26 mL, 4.52 mmol, 20.0 equiv.) was stirred for 15 min at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for an additional 1.5 h. The reaction mixture was filtered under a positive stream of argon and the resulting residue was thoroughly washed with diethyl ether. Column chromatography (DCM/MeOH: 92:8) of the brownish residue gave rise to 0.076 g (89%) of **28** as a white powder: m.p. 50–60 °C (hygroscopic); ^{1}H NMR (DMSO-d_6) δ 11.0 (s, 1H), 7.49 (d, 1H, $J = 7.8$ Hz), 7.36 (d, 1H, $J = 8.0$ Hz), 7.26 (d, 1H, $J = 2.3$ Hz), 7.09 (t, 1H, $J = 7.0$ Hz), 6.99 (t, 1H, $J = 7.0$ Hz), 5.70 (t, 1H, $J = 5.7$ Hz), 4.52 (s, 2H), 3.79 (s, 2H), 3.64 (s, 3H), 3.60 (d, 1H, $J = 5.5$ Hz), 3.51 (dd, 1H, $J = 15.8$, 5.7 Hz), 3.40 (dd, 1H, $J = 13.4$, 4.4 Hz), 3.33 (dd, 1H, $J = 13.4$, 7.9 Hz), 3.05–2.98 (m, 1H), 2.45 (d, 2H, $J = 5.7$ Hz); ^{13}C NMR (DMSO-d_6) δ 172.1, 171.1, 139.9, 136.1, 127.0, 124.1, 121.5, 121.0, 118.4, 118.3, 111.4, 106.7, 67.2, 52.0, 48.6, 43.2, 39.4, 30.7, 29.3; MS (EI) *m/z* 342 (5, M^+), 167 (100), 154 (18), 130 (86), 108 (46); HRMS (EI) *m/z* calcd for $C_{19}H_{22}N_2O_4$: 342.157957; found: 342.158371.

4.2.15. 5-(tert-Butyl-dimethyl-silanyloxymethyl)-3-hydroxymethyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid tert-butyl ester (**29**)

DIBAL-H (8.9 mL of a 1.5 M solution in toluene, 13.20 mmol, 2.2 equiv.) was added dropwise over a period of 45 min to a stirred solution of **12** (2.398 g, 6.00 mmol, 1.0 equiv.) in THF (15 mL) at −78 °C. After 3 h the reaction mixture was slowly warmed to 0 °C, stirred for 30 min and then carefully quenched by addition of 1 mL H_2O in 5 mL of THF. Subsequent addition of 25 mL diethyl ether and 20 mL of saturated Rochelle's solution (potassium sodium L-tartrate tetrahydrate in water) produced a gelatine-like solid, which, after addition of 10 mL of a saturated NH_4Cl-solution, was stirred at room temperature until the slurry re-dissolved and a separation of the layers was observed (30 min). The aqueous layer was extracted three times with diethyl ether and the combined organic layers were washed twice with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (hexane/ethyl acetate: 2:1) gave rise to 1.684 g (76%) of **29** as colourless oil: ^{1}H NMR δ (rotamers, ratio: 2.4:1) 5.77–5.71 (m, 0.7H), 5.69–5.66 (m, 0.3H), 4.18 (dd, 0.7H, $J = 16.3$, 6.0 Hz), 4.05 (dd, 0.8H, $J = 14.4$, 3.7 Hz), 4.00 (bs, 0.3H), 3.98–3.95 (m, 1H), 3.94 (s, 1.2H), 3.77 (s, 0.7H), 3.60–3.54 (m, 1.5H), 3.57–3.43 (m, 1.5H), 3.36–3.29 (m, 0.7H), 3.16 (dd, 0.8H, $J = 14.3$, 4.0 Hz), 3.01 (pst, 0.2H), 2.41 (d, 0.3H, $J = 14.4$ Hz), 2.27 (d, 0.7H, $J = 14.4$ Hz), 2.21–2.00 (m, 2.1H), 1.44 (s, 2.7H), 1.43 (s, 6.3H), 0.89 (s, 9H), 0.07 (s, 2.1H), 0.05 (s, 4.8H); ^{13}C NMR δ (rotamers) 156.2, 155.1, 141.2, 138.9, 123.2, 121.1, 79.7, 79.4, 68.9, 67.5, 63.8, 62.3, 49.3, 49.0, 46.4, 39.6, 38.8, 29.6, 28.6, 28.3, 28.2, 25.7, 18.3, 18.2, −5.5; MS (ES+) m/z 394 (14, $[M+Na]^+$), 765 (100, $[2M+Na]^+$), 1136 (15, $[3M+Na]^+$); HRMS (ES+) m/z calcd for $C_{19}H_{38}NO_4Si$: 372.257012; found: 372.256321.

4.2.16. 3,5-Bis-hydroxymethyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid tert-butyl ester (**30**)

Compound **29** (0.615 g, 1.66 mmol, 1.0 equiv.) was dissolved in a 30:1 mixture of THF and aqueous HCl 32% and stirred at room temperature for 20 min. After addition of a saturated $NaHCO_3$-solution, the reaction mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. Column chromatography (ethyl acetate) of the oily residue afforded 0.370 g (87%) of **30** as colourless oil: ^{1}H NMR (rotamers, ratio: ~1.6:1) δ 5.80 (bs, 0.39H), 5.75 (bs, 0.61H), 4.19 (dd, 0.61H, $J = 16.5$, 5.7 Hz), 4.07–3.95 (m, 2.96H), 3.84 (bd, 0.83H, $J = 16.9$ Hz), 3.66–3.47 (m, 2.40H), 3.45–3.37 (m, 1H), 3.22 (dd, 0.86H, $J = 14.3$, 4.2 Hz), 2.47 (d, 0.37H, $J = 15.1$ Hz), 2.39–2.29 (m, 1H), 2.25 (dd, 1.2H, $J = 15.0$, 6.7 Hz), 2.18–2.06 (bs, 1H), 1.46 (s, 9H); ^{13}C NMR (rotamers) δ 156.1, 155.4, 141.4, 140.1, 124.3, 122.6, 80.0, 79.8, 68.2, 67.7, 63.3, 63.1, 49.7, 49.3, 46.4, 46.0, 39.4, 38.8, 29.5, 29.0, 28.3, 28.2; MS (ES+) m/z 280 (100, $[M+Na]^+$), 537 (70, $[2M+Na]^+$); HRMS (ES+) m/z calcd for $C_{13}H_{23}NO_4Na$: 280.152478; found: 280.152423.

4.2.17. 3,5-Bis-benzoyloxymethyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid tert-butyl ester (**31**)

To a stirred solution of **30** (0.732 g, 2.84 mmol, 1.0 equiv.) in DCM (20 mL) were added TEA (1.03 mL, 7.38 mmol, 2.6 equiv.) and a catalytic amount of DMAP at 0 °C. The reaction mixture was allowed to reach room temperature followed by the dropwise addition of a solution of benzoylchloride (0.726 mL, 6.25 mmol, 2.2 equiv.) and stirred for 14 h at ambient temperature. After addition of *t*-BuOMe the reaction mixture was quenched with a saturated NH_4Cl-solution and the aqueous layer was extracted twice with *t*-BuOMe. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (hexane/*t*-BuOMe: 8:2) of the remaining oily residue afforded 0.985 g (75%) of **31** as a colourless oil: ^{1}H NMR δ 8.02 (d, 2H, $J = 7.3$ Hz), 8.0 (d, 2H, $J = 7.1$ Hz), 7.58–7.50 (m, 2H), 7.44–7.34 (m, 4H), 5.95–5.87 (m, 1H), 4.73 (dd, 2H, $J = 12.8$, 4.8 Hz), 4.36–4.27 (m, 1H), 4.23 (dd, 1H, $J = 11.0$, 6.9 Hz), 4.14–3.96 (m, 2H), 3.80–3.65 (m, 1H), 3.50 (dd, 1H, $J = 14.3$, 7.3 Hz), 2.57–2.42 (m, 2H), 2.34 (dd, 1H, $J = 15.6$, 8.7 Hz), 1.46 (s, 9H); ^{13}C NMR δ (rotamers) 166.2, 166.1, 155.4, 155.2, 135.7, 134.8, 132.9, 129.9, 129.47, 129.42, 128.31, 128.25, 127.2, 126.9, 80.0, 79.7, 69.4, 66.7, 66.5, 49.2, 46.2, 37.1, 37.0, 30.0, 29.5, 28.3; MS (ES+) m/z 488 (100, $[M+Na]^+$), 504 (30, $[M+K]^+$); HRMS (ES+) m/z calcd for $C_{27}H_{31}NO_6Na$: 488.204908; found: 488.203494.

4.2.18. 3,5-Bis-benzoyloxymethyl-2,3,4,7-tetrahydro-1H-azepinium chloride (**32**)

A suspension of **31** (0.266 g, 0.57 mmol, 1.0 equiv.) in a 2 M solution of hydrogen chloride in diethyl ether (5.71 mL, 11.42 mmol, 20.0 equiv.) was stirred for 16 h at room temperature. The resulting precipitate was separated by filtration under a positive stream of argon, washed several times with dry diethyl ether and dried to give rise to 0.172 g (75%) of **32** as a colourless powder: m.p. 175–180 °C; ^{1}H NMR (DMSO-d_6) δ 9.60–9.43 (bs, 1H), 9.34–9.08 (bs, 1H), 8.01–7.95 (sm, 4H), 7.70–7.63 (sm, 2H), 7.55–7.47 (sm, 4H), 5.96–5.91 (pst, 1H), 4.80 (s, 2H), 4.31–4.24 (sm, 2H), 3.79 (dd, 1H, $J = 15.6$, 6.0 Hz), 3.73 (dd, 1H, $J = 15.5$, 5.6 Hz), 3.51–3.46 (sm, 1H), 3.26, 3.19 (sm, 1H), 2.65–2.57 (sm, 1H), 2.49–2.45 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 165.4, 165.2, 141.2, 133.4, 133.3, 129.3, 129.1, 128.7, 128.6, 120.7, 67.7, 66.1, 49.4, 42.5, 33.3, 30.4; MS (ES+) m/z 366 (100, $[M+H]^+$); HRMS (ES+) m/z calcd for $C_{22}H_{24}NO_4$: 366.170534; found: 366.172069.

4.2.19. 5-(tert-Butyl-dimethyl-silanyloxymethyl)-3-(2-1H-indol-3-yl-acetoxymethyl)-2,3,4,7-tetrahydro-azepine-1-carboxylic acid tert-butyl ester (**33**)

To a stirred solution of indole-3-acetic acid (0.420 g, 2.40 mmol, 1.2 equiv.) in a 1:1 mixture of THF and

DCM were added **29** dissolved in a 1:1 mixture of THF and DCM (0.743 g, 2.00 mmol, 1.0 equiv.) and DMAP (0.012 g, 0.10 mmol, 5 mol%) followed by the addition of DCC (0.536 g, 2.60 mmol, 1.3 equiv.) in a 1:1 mixture of THF and DCM. The reaction mixture was stirred at room temperature for 14 h and then carefully quenched by addition of a saturated $NaHCO_3$-solution. After addition of diethyl ether the layers were separated. The organic layer was filtered and the residue was washed three times with diethyl ether. The combined filtrates were washed twice with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (hexane/*t*-BuOMe: 1.5:1) afforded 0.865 g (82%) of **33** as a colourless oil: ^{1}H NMR δ 8.12 (bs, 1H), 7.60 (d, 1H, $J = 7.9$ Hz), 7.34 (d, 1H, $J = 7.9$ Hz), 7.22–7.10 (m, 3H), 5.67 (d, 1H, $J = 14.7$ Hz), 4.05–3.91 (m, 3H), 3.85 (s, 3H), 3.77 (s, 2H), 3.59 (d, 0.5H, $J = 12.2$ Hz), 3.49 (d, 0.5H, $J = 12.8$ Hz), 3.27 (dd, 1H, $J = 14.1$, 7.9 Hz), 2.19 (bs, 1H), 2.13–1.90 (m, 2H), 1.42 (s, 9H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (rotamers) δ 172.0, 155.4, 155.2, 140.3, 138.9, 136.1, 127.1, 123.2, 123.1, 122.0, 121.9, 121.6, 121.5, 119.4, 118.7, 118.6, 111.23, 111.18, 107.9, 79.7, 79.5, 67.4, 67.0, 66.8, 66.4, 49.5, 49.1, 46.2, 46.0, 36.8, 36.3, 31.2, 29.3, 28.6, 28.4, 25.8, 18.3, −5.35, −5.41; MS (ES+) *m/z* 546 (90, $[M+NH_4]^+$), 1075 (100, $[2M+H+NH_4]^+$); HRMS (ES+) *m/z* calcd for $C_{29}H_{48}N_3O_5Si$: 546.336326; found: 546.333278.

4.2.20. 5-Hydroxymethyl-3-(2-1H-indol-3-yl-acetoxymethyl)-2,3,4,7-tetrahydro-azepine-1-carboxylic acid tert-butyl ester (*34*)

Compound **33** (0.633 g, 1.20 mmol, 1.0 equiv.) was dissolved in a 30:1 mixture of THF and aqueous HCl 32% and stirred at room temperature for 40 min. After addition of a saturated $NaHCO_3$-solution, the reaction mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (hexane/*t*-BuOMe: 1:4) afforded 0.424 g (85%) of **34** as a colourless oil: ^{1}H NMR δ 8.23 (s, 1H), 7.62 (d, 1H, $J = 7.8$ Hz), 7.63 (d, 1H, $J = 8.0$ Hz), 7.20 (t, 1H, $J = 7.4$ Hz), 7.17 (d, 1H, $J = 1.8$ Hz), 7.14 (d, 1H, $J = 7.2$ Hz), 5.63 (t, 1H, $J = 4.4$ Hz), 4.08–4.01 (m, 1H), 3.97 (dd, 1H, $J = 14.8$, 7.6 Hz), 3.94–3.85 (bm, 2H), 3.79 (s, 2H), 3.75 (d, 2H, $J = 7.10$ Hz), 3.61–3.45 (bm, 1H), 3.30 (dd, 1H, $J = 14.0$, 7.8 Hz), 2.30–2.18 (bs, 1H), 2.18–2.07 (bm, 1H), 1.99 (dd, 1H, $J = 15.0$, 8.1 Hz), 1.58 (bs, 1H), 1.44 (s, 9H); ^{13}C NMR δ (rotamers) 172.0, 155.3, 140.5, 139.6, 136.1, 127.1, 123.31, 123.25, 122.8, 122.0, 121.9, 119.4, 118.7, 118.6, 111.3, 107.9, 79.9, 79.7, 67.6, 67.4, 66.4, 49.3, 49.2, 46.1, 36.8, 36.3, 31.3, 29.3, 29.0, 28.4; MS (ES+) *m/z* 437 (100, $[M+Na]^+$), 851 (56, $[2M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{23}H_{31}N_2O_5$: 415.223297; found: 415.221057.

4.2.21. 3-(2-1H-Indol-3-yl-acetoxymethyl)-5-(4-propyl-benzoyloxymethyl)-2,3,4,7-tetrahydro-azepine-1-carboxylic acid tert-butyl ester (*35a*)

To a solution of **34** (0.480 g, 1.16 mmol, 1.0 equiv.), *N*-ethyl diisopropylamine (0.236 mL, 1.51 mmol, 1.3 equiv.) and a catalytic amount of DMAP in DCM at 0 °C, a solution of 4-propyl-benzoyl chloride in DCM (0.214 mL, 1.28 mmol, 1.1 equiv.) was added dropwise over a period of 30 min. The reaction mixture was allowed to slowly reach room temperature and stirred for additional 14 h. After careful addition of a saturated NH_4Cl-solution, the reaction mixture was extracted three times with *t*-BuOMe. The combined organic layers were washed twice with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (hexane/*t*-BuOMe: 1:1) gave rise to 0.395 g (61%) of **35a** as colourless oil: ^{1}H NMR δ 8.14 (s, 1H), 7.95 (d, 2H, $J = 8.0$ Hz), 7.59 (d, 1H, $J = 8.0$ Hz), 7.32 (d, 1H, $J = 8.0$ Hz), 7.24 (d, 2H, $J = 8.3$ Hz), 7.17 (t, 1H, $J = 7.4$ Hz), 7.13–7.08 (m, 2H), 5.79 (s, 1H), 4.51 (s, 2H), 4.13–4.07 (m, 1H), 3.96 (dd, 2H, $J = 11.0$, 7.8 Hz), 3.92–3.84 (m, 1H), 3.74 (s, 2H), 3.62–3.46 (m, 1H), 3.32 (dd, 1H, $J = 14.1$, 7.9 Hz), 2.63 (t, 2H, $J = 7.7$ Hz), 2.33–2.15 (m, 2H), 2.13–2.03 (m, 1H), 1.65 (sex, 2H, $J = 7.5$ Hz), 1.44 (s, 9H), 0.94 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (rotamers) δ 171.9, 166.3, 155.4, 155.2, 148.4, 136.04, 135.97, 134.7, 129.6, 128.5, 127.4, 127.1, 126.6, 126.1, 123.1, 122.1, 122.0, 119.5, 118.7, 111.2, 108.1, 80.0, 79.8, 69.1, 66.3, 49.2, 49.0, 46.2, 46.0, 37.9, 36.9, 36.5, 31.3, 29.8, 29.2, 28.4, 24.2, 13.7; MS (ES+) *m/z* 583 (100, $[M+Na]^+$), 1144 (71, $[2M+H+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{33}H_{44}N_3O_6$ ($[M+NH_4]^+$): 578.323012; found: 578.322479.

4.2.22. 3-(2-1H-Indol-3yl-acetoxymethyl)-2,3,4,7-tetrahydro-azepine-1-carboxylic acid tert-butyl-ester (*35b*)

To a solution of **34** (0.843 g, 2.03 mmol, 1.0 equiv.), triethylamine (0.4 mL, 2.85 mmol, 1.4 equiv.) and a catalytic amount of DMAP in DCM at room temperature, a solution of acetyl chloride in DCM (0.174 mL, 2.44 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred for 4 h at ambient temperature. After careful addition of a saturated NH_4Cl-solution, the reaction mixture was extracted three times with diethyl ether. The combined organic layers were washed twice with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (hexane/*t*-BuOMe: 1:1) gave rise to 0.730 g (79%) of **35b** as colourless oil: ^{1}H NMR δ 8.24 (s, 1H), 7.61 (d, 1H, $J = 8.0$ Hz), 7.35 (pst, 1H), 7.23–7.10 (m, 3H), 5.73–5.67 (bs, 1H), 4.29 (s, 2H), 4.09–4.01 (m, 1H), 4.00–3.92 (m, 2H), 3.88–3.82 (m, 1H), 3.79 (s, 2H), 3.61–3.47 (sm, 1H), 3.34–2.95 (sm, 1H), 2.33–2.22 (bm, 1H), 2.21–2.10 (sm, 1H), 2.04 (s, 3H), 2.07–1.97 (bm, 1H), 1.44 (s, 9H); ^{13}C NMR (rotamers) δ 171.9, 170.7, 155.3, 155.2, 136.1, 135.6, 134.5, 127.1, 126.7, 126.3, 123.1, 122.1, 122.0, 119.5, 118.73, 118.65, 111.25, 111.18, 108.1, 79.9, 79.7, 68.9, 66.4, 49.0, 46.1, 46.0, 36.7, 36.3, 31.3, 29.7, 29.6, 29.2, 28.4, 28.1, 20.8;

MS (ES+) *m/z* 479 (86, $[M+Na]^+$), 935 (100, $[2M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{25}H_{32}N_2O_6Na$: 479.215807; found: 479.213201.

4.2.23. 3-(2-1H-Indol-3-yl-acetoxymethyl)-5-(4-propyl-benzoyloxymethyl)-2,3,4,7-tetrahydro-1H-azepinium chloride (**36a**)

A solution of **35a** (0.250 g, 0.45 mmol, 1.0 equiv.) in a 2 M solution of hydrogen chloride in diethyl ether (4.5 mL, 8.92 mmol, 20.0 equiv.) was stirred for 3 h at room temperature. The reaction mixture was filtered under a positive stream of argon, and the resulting residue was washed four times with diethyl ether to give rise to 0.205 g (92%) of **36a** as white powder: m.p. 135–140 °C; ^{1}H NMR (DMSO-d_6) δ 10.99 (s, 1H), 9.50–9.00 (bs, 1.5H), 7.91 (d, 2H, $J = 7.3$ Hz), 7.48 (d, 1H, $J = 7.3$ Hz), 7.40–7.30 (m, 3H), 7.23 (s, 1H), 7.07 (t, 1H, $J = 6.9$ Hz), 6.98 (t, 1H, $J = 7.1$ Hz), 5.86 (s, 1H), 4.67 (s, 2H), 4.01 (d, 2H, $J = 4.8$ Hz), 3.73 (s, 3H), 3.68–3.56 (m, 1H), 3.43–3.20 (m, 1H, overlapping with H_2O), 3.04 (sm, 1H), 2.62 (t, 2H, $J = 7.2$ Hz), 2.45–2.35 (m, 1H), 2.30 (psd, 2H, $J = 14.4$ Hz), 1.63–1.53 (m, 2H), 0.88 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (DMSO-d_6) δ 169.2, 163.0, 146.1, 139.4, 133.9, 127.1, 126.6, 124.8, 121.9, 118.9, 118.1, 116.3, 116.2, 109.3, 104.5, 65.4, 63.3, 47.4, 40.6, 35.0, 31.1, 28.4, 28.1, 21.5, 11.4; MS (ES+) *m/z* 461 (100, $[M+H]^+$), 921 (5, $[2M+H]^+$); HRMS (ES+) *m/z* calcd for $C_{28}H_{33}N_2O_4$: 461.244033; found: 461.240402. Anal. Calc. for $C_{28}H_{32}N_2O_4 \cdot HCl \cdot 1.5H_2O$: C, 64.17; H, 6.83; N, 5.35; found: C, 64.52; H, 6.55; N, 5.26%.

4.2.24. 5-Acetoxymethyl-3-(2-1H-indol-3-yl-acetoxymethyl)-2,3,4,7-tetrahydro-1H-azepinium chloride (**36b**)

A solution of **35b** (0.345 g, 0.76 mmol, 1.0 equiv.) in a 2 M solution of hydrogen chloride in diethyl ether (7.6 mL, 15.11 mmol, 20.0 equiv.) was stirred for 8 h at room temperature. The reaction mixture was filtered under a positive stream of argon and the resulting residue was thoroughly washed with diethyl ether. Column chromatography (DCM/MeOH: 92:8) of the brownish residue gave rise to 0.197 g (66%) of **36b** as a white, hygroscopic powder: m.p. 35–40 °C; ^{1}H NMR (DMSO-d_6) δ 10.99 (s, 1H), 9.35 (bs, 1H), 9.05 (bs, 1H), 7.50 (d, 1H, $J = 7.8$ Hz), 7.36 (d, 1H, $J = 8.3$ Hz), 7.26 (d, 1H, $J = 2.3$ Hz), 7.08 (t, 1H, $J = 7.5$ Hz), 7.00 (t, 1H, 7.0 Hz), 5.74 (t, 1H, $J = 5.3$ Hz), 4.40 (s, 2H), 3.99 (d, 2H, $J = 6.0$ Hz), 3.78 (s, 2H), 3.73–3.65 (m, 1H), 3.64–3.54 (m, 1H), 3.07–2.96 (m, 1H), 2.35–2.16 (m, 3H), 2.09–1.99 (m, 1H), 2.04 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 171.4, 169.8, 141.4, 136.1, 127.0, 124.0, 121.0, 119.8, 118.5, 118.4, 111.4, 106.7, 66.8, 65.3, 49.4, 42.5, 33.1, 30.6, 30.0, 20.5; MS (ES+) *m/z* 357 (100, $[M+H]^+$); HRMS (ES+) *m/z* calcd for $C_{20}H_{25}N_2O_4$: 357.181433; found: 357.181830.

4.2.25. 5-Hydroxymethyl-3-(2-1H-indol-3-yl-acetoxymethyl)-2,3,4,7-tetrahydro-1H-azepinium chloride (**37**)

A suspension of **34** (0.450 g, 1.10 mmol, 1.0 equiv.) in a 2 M solution of hydrogen chloride in diethyl ether (8.2 mL, 16.30 mmol, 15.0 equiv.) was stirred for 15 min at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for an additional 1.5 h. The suspension was filtered under a positive stream of argon and the resulting residue was thoroughly washed with diethyl ether. Column chromatography (DCM/MeOH: 8:2) of the brownish residue yielded 0.360 g (93%) of **37** as a white, hygroscopic powder: m.p. 40-50 °C; ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 9.40–8.90 (bs, 2H), 7.51 (d, 1H, $J = 7.8$ Hz), 7.36 (d, 1H, $J = 8.0$ Hz), 7.26 (d, 1H, $J = 2.5$ Hz), 7.08 (t, 1H, $J = 7.0$ Hz), 7.00 (t, 1H, $J = 7.1$ Hz), 5.68 (t, 1H, $J = 5.5$ Hz), 5.10–5.00 (bs, 1H), 3.98 (d, 2H, $J = 4.8$ Hz), 3.78 (s, 2H), 3.76 (s, 2H), 3.66 (dd, 1H, $J = 15.4$, 6.2 Hz), 3.54 (dd, 1H, $J = 15.4$, 5.7 Hz), 2.98 (dd, 1H, $J = 13.1$, 9.9 Hz), 2.26–2.13 (m, 2H), 2.08 (d, 1H, $J = 14.0$ Hz); ^{13}C NMR (DMSO-d_6) δ 171.4, 147.2, 136.1, 127.0, 124.0, 121.0, 118.5, 118.4, 115.4, 111.4, 106.7, 65.5, 64.5, 49.7, 42.9, 33.3, 30.6, 29.9; MS (EI) *m/z* 314 (10, M^+), 130 (55); HRMS (EI) *m/z* calcd for $C_{18}H_{22}N_2O_3$: 314.163043; found: 314.163128.

4.2.26. 6-Hydroxymethyl-2,3,4,7-tetrahydro-azepine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester (**38**)

Compound **20** (0.850 g, 2.13 mmol) was dissolved in a 30:1 mixture of THF and aqueous HCl 32% and stirred at room temperature for 40 min. After addition of a saturated $NaHCO_3$-solution, the reaction mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. Column chromatography of the oily residue afforded 0.481 g (80%) of **38** as colourless oil: ^{1}H NMR δ (rotamers, ratio: ~3:1) 5.83 (t, 0.75H, $J = 6.0$ Hz), 5.79–5.74 (bs, 0.24H), 4.12–4.01 (m, 4H), 3.95 (d, 0.74H, $J = 12.1$ Hz), 3.75 (s, 0.6H), 3.73–3.67 (m, 3.6H), 3.59–3.51 (sm, 0.21H), 3.45 (dd, 0.69H, $J = 14.0$, 9.6 Hz), 2.72–2.64 (m, 1.26H), 2.57–2.48 (m, 1.28H), 2.48–2.39 (m, 1H), 1.46 (s, 9H); ^{13}C NMR δ (rotamers) 173.9, 173.6, 155.5, 155.1, 142.9, 141.4, 125.9, 124.2, 80.6, 80.0, 66.3, 66.1, 51.85, 51.79, 50.8, 48.9, 47.5, 47.4, 43.0, 42.7, 28.25, 28.20, 27.4; MS (ES+) *m/z* 308 (56, $[M+Na]^+$), 593 (100, $[2M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{14}H_{23}NO_5Na$: 308.147393; found: 308.148530.

4.2.27. 6-(2-1H-Indol-3-yl-acetoxymethyl)-2,3,4,7-tetrahydro-azepine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester (**39**)

To a stirred solution of indole-3-acetic acid (0.252 g, 1.44 mmol, 1.2 equiv.) in a 1:1 mixture of THF and DCM were added **38** dissolved in above described mixture (0.342 g, 1.20 mmol, 1.0 equiv.) and DMAP (0.008 g, 0.06 mmol, 5 mol%) followed by the addition of DCC (0.322 g, 1.56 mmol, 1.3 equiv.) in a 1:1 mixture of THF

and DCM. The reaction mixture was stirred at room temperature for 16 h. After careful addition of a saturated $NaHCO_3$-solution, the reaction mixture was extracted three times with diethyl ether, the combined organic layers were washed twice with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (hexane/ethyl acetate: 3:1) afforded 0.510 g (96%) of **39** as a colourless oil: ^{1}H NMR δ (rotamers, ratio: ~1:1) 8.20 (psd, 1H, $J = 7.6$ Hz), 7.61 (d, 1H, $J = 7.8$ Hz), 7.35 (t, 1H, $J = 7.8$ Hz), 7.22–7.11 (m, 3H), 5.75 (dd, 1H, $J = 12.3$, 6.0 Hz), 4.53 (m, 2H), 4.06 (d, 0.5H, $J = 17.2$ Hz), 3.95–3.87 (m, 1H), 3.84 (d, 0.5H, $J = 17.2$ Hz), 3.79 (d, 2H, $J = 2.8$ Hz), 3.76–3.71 (m, 1H). 3.69 (s, 1.57H), 3.67 (s, 1.44H), 3.56–3.50 (sm, 1H), 2.88–2.81 (m, 1H), 2.46–2.38 (m, 2H), 1.46 (s, 4.41H), 1.43 (s, 4.57H); ^{13}C NMR δ (rotamers) 173.84, 173.76, 171.6, 155.2, 155.1, 136.7, 136.1, 135.9, 127.7, 127.14, 127.08, 126.7, 123.2, 123.1, 122.1, 122.0, 119.54, 119.50, 118.8, 118.7, 111.2, 111.1, 108.1, 80.1, 67.9, 51.9, 48.6, 48.3, 48.1, 47.7, 43.2, 42.6, 31.30, 31.26, 28.35, 28.30, 27.3, 26.1; MS (ES+) m/z 465 (100, $[M+Na]^+$), 907 (74, $[2M+Na]^+$); HRMS (ES+) m/z calcd for $C_{24}H_{34}N_3O_6$ ($[M+NH_4]^+$): 460.244761; found: 460.244144.

4.2.28. 6-(2-1H-Indol-3-yl-acetoxymethyl)-3-methoxycarbonyl-2,3,4,7-tetrahydro-1H-azepinium chloride (*40*)

A solution of **39** (0.372 g, 0.84 mmol, 1.0 equiv.) in a 2 M solution of hydrogen chloride in diethyl ether (8.41 mL, 1.82 mmol, 20.0 equiv.) was stirred for 20 min at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for an additional 3 h. The reaction mixture was filtered under a positive stream of argon and thoroughly washed with diethyl ether. Column chromatography (DCM/MeOH: 92:8) of the brownish residue afforded 0.292 g (92%) of **40** as a white, hygroscopic powder: m.p. 50–60 °C; ^{1}H NMR (DMSO-d_6) δ 11.0 (s, 1H), 9.50–9.10 (bs, 2H), 7.49 (d, 1H, $J = 8.0$ Hz), 7.36 (d, 1H, $J = 8.0$ Hz), 7.25 (d, 1H, $J = 2.3$ Hz), 7.08 (d, 1H, $J = 7.1$ Hz), 7.00 (d, 1H, $J = 7.1$ Hz), 6.03 (t, 1H, $J = 6.2$ Hz), 4.52 (s, 2H), 3.78 (s, 2H), 3.67 (d, 1H, $J = 15.6$ Hz), 3.64 (s, 3H), 3.60 (d, 1H, $J = 15.6$ Hz), 3.47 (dd, 1H, $J = 13.4$, 4.1 Hz), 3.40–3.33 (m, 1H), 3.06–2.98 (sm, 1H), 2.64–2.58 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 171.9, 171.2, 136.0, 132.1, 130.9, 127.0, 124.1, 121.0, 118.44, 118.37, 111.4, 106.7, 66.8, 52.1, 18.4, 44.6, 39.1, 30.6, 27.4; MS (EI) m/z 342 (20, M^+), 168 (68), 130 (100), 108 (72); HRMS (ES+) m/z calcd for $C_{19}H_{22}N_2O_4$: 342.157957; found: 342.157728. Anal. Calc. for $C_{19}H_{22}N_2O_4 \cdot HCl \cdot 1H_2O$: C, 57.50; H, 6.35; N, 7.06.; found: C, 57.20; H, 6.34; N, 7.09%.

Acknowledgements

We gratefully acknowledge the financial support of our research by the Deutsche Pharmazeutische Gesellschaft (DPhG) within the fellowship "DPhG Stiftung zur Förderung des wissenschaftlichen Nachwuchses" for W.E.D. The authors in particular would like to thank Prof. Dr. G. Klebe, Philipps-Universität Marburg, for his generous support of their research.

References

[1] (a) For recent reviews on ring closing metathesis see: M. Schuster, S. Blechert, Angew. Chem., Int. Ed. 36 (1997) 2036–2056;
(b) R.H. Grubbs, S. Chang, Tetrahedron 54 (1998) 4413–4450;
(c) A. Fürstner, Top. Organomet. Chem. 1 (1998) 37–72;
(d) A. Fürstner, Angew. Chem., Int. Ed. 39 (2000) 3012–3043;
(e) T.M. Trnka, R.H. Grubbs, Acc. Chem. Res. 34 (2001) 18–29.
[2] Available from: <http://nobelprize.org/nobel_prizes/chemistry/laureates/2005/press.html>.
[3] (a) For reviews see: A.J. Phillips, A.D. Abell, Aldrichim. Acta 32 (1999) 75–89;
(b) A. Nadin, J. Chem. Soc., Perkin Trans. 1 (1998) 3493–3513;
(c) A. Mitchinson, A. Nadin, J. Chem. Soc., Perkin Trans. 1 (1999) 2553–2581;
(d) A. Mitchinson, A. Nadin, J. Chem. Soc., Perkin Trans. 1 (2000) 2862–2892;
(e) F.-X. Felpin, J. Lebreton, Eur. J. Org. Chem. (2003) 3693–3712;
(f) A. Deiters, S.F. Martin, Chem. Rev. 104 (2004) 2199–2238.
[4] S. Brass, H.-D. Gerber, S. Dörr, W.E. Diederich, Tetrahedron 62 (2006) 1777–1786.
[5] (a) B. Greenwood, T. Mutabingwa, Nature 415 (2002) 670–672;
(b) J. Sachs, P. Malaney, Nature 415 (2002) 680–685;
(c) R.W. Snow, M. Craig, U. Deichmann, K. Marsh, Bull. World Health Organ. 77 (1999) 624–640;
(d) World Health Organisation/UNICEF The Africa Malaria report (2003) 1–112.
[6] C. Laurent, A. Bourgeois, M. Mpoudi, C. Butel, M. Peeters, E. Mpoudi-Ngole', E. Delaporte, Emerg. Infect. Dis. 10 (2004) 1953–1956.
[7] (a) S.E. Francis, D.J. Sullivan Jr., D.E. Goldberg, Annu. Rev. Microbiol. 51 (1997) 97–123;
(b) G.H. Coombs, J.C. Mottram, Parasitology 114 (Suppl.) (1997) S61–S80;
(c) D. Leung, G. Abbenante, D.P. Fairlie, J. Med. Chem. 43 (2000) 305–341;
(d) K.A. Werbovetz, Curr. Med. Chem. 7 (2000) 835–860;
(e) P.J. Rosenthal, Emerg. Infect. Dis. 4 (1998) 49–57.
[8] (a) S.E. Francis, I.Y. Gluzman, A. Oksman, A. Knickerbocker, R. Mueller, M.L. Bryant, D.R. Sherman, D.G. Russell, D.E. Goldberg, EMBO J. 13 (1994) 306–317;
(b) R. Banerjee, J. Liu, W. Beatty, L. Pelosof, M. Klemba, D.E. Goldberg, Proc. Natl. Acad. Sci. USA 99 (2002) 990–995;
(c) K. Ersmark, I. Feierberg, S. Bjelic, E. Hamelink, F. Hackett, M.J. Blackman, J. Hulten, B. Samuelsson, J. Aqvist, A. Hallberg, J. Med. Chem. 47 (2004) 110–122;
(d) J. Liu, I.Y. Gluzman, M.E. Drew, D.E. Goldberg, J. Biol. Chem. 280 (2005) 1432–1437.
[9] E. De Clercq, J. Med. Chem. 48 (2005) 1297–1313.
[10] (a) D. Leung, G. Abbenante, D.P. Fairlie, J. Med. Chem. 43 (2000) 305–341;
(b) D.H. Rich, J. Med. Chem. 28 (1985) 263–273;
(c) J.B. Cooper, Current Drug Targets 3 (2002) 155–173.
[11] E. Specker, J. Böttcher, S. Brass, A. Heine, H. Lilie, A. Schoop, G. Müller, N. Griebenow, G. Klebe, ChemMedChem 1 (2006) 106–117.
[12] E. Specker, J. Böttcher, H. Lilie, A. Heine, A. Schoop, G. Müller, N. Griebenow, G. Klebe, Angew. Chem., Int. Ed. 44 (2005) 3140–3144.
[13] (a) Compound **13** has already been synthesized via a different sequence: A. Khazaei, R.G. Vaghei, E. Karkhanei, Synth. Commun. 32 (2002) 2107–2113;
(b) P.B. Anzeveno, J.A. Campbell, W.L. White, Synth. Commun. 16 (1986) 387–392;

(c) H. Saimoto, K. Nishio, H. Yamamoto, M. Shinoda, T. Hiyama, H. Nozaki, Bull. Chem. Soc. Jpn. 56 (1983) 3093–3098;
(d) H. Duettmann, P. Weyerstahl, Chem. Ber. 112 (1979) 3480–3485.
[14] H.D. Maynard, R.H. Grubbs, Tetrahedron Lett. 40 (1999) 4137–4140.
[15] For a representative procedure see: T.A. Kirkland, R.H. Grubbs, J. Org. Chem. 62 (1997) 7310–7318.
[16] (a) Compound **21** has already been described in the literature: A.B. Smith III, P.A. Levenberg, P.J. Jerris, R.M. Scarborough, P.M. Wovkulich, J. Am. Chem. Soc. 103 (1981) 1501–1513, the described method seems to be less convenient;
(b) S. Brandau, R. Fröhlich, D. Hoppe, Tetrahedron Lett. 46 (2005) 6709–6711.
[17] (a) M. Scholl, S. Ding, C.W. Lee, R.H. Grubbs, Org. Lett. 1 (1999) 953–956;
(b) U. Majumder, J.M. Cox, J.D. Rainier, Org. Lett. 5 (2003) 913–916;
(c) A.K. Chatterjee, F.D. Toste, S.D. Goldberg, R.H. Grubbs, Pure Appl. Chem. 75 (2003) 421–425;
(d) M. Marhold, A. Buer, H. Hiemstra, J.H.v. Maarseveen, G. Haufe, Tetrahedron Lett. 45 (2004) 57–60.
[18] (a) A. Taylor, D.P. Brown, S. Kadam, M. Maus, W.E. Kohlbrenner, D. Weigl, M.C. Turon, L. Katz, Appl. Microbiol. Biotechnol. 37 (1992) 205–210;
(b) M.V. Toth, G.R. Marshall, Int. J. Pept. Prot. Res. 36 (1990) 544–550.
[19] S. Weik, T. Luksch, A. Evers, J. Böttcher, C.A. Sotriffer, A. Hasilik, H.-G. Löffler, G. Klebe, J. Rademann, ChemMedChem 1 (2006) 445–457.
[20] Y.M. Ahn, K.-L. Yang, G.I. Georg, Org. Lett. 3 (2001) 1411–1413.