Scaffold Diversity through Intramolecular Cascade Reactions of Solid-Supported Cyclic *N*-Acyliminium Intermediates

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Received June 22, 2007

The solid-phase synthesis of pharmacologically interesting heterocycles is presented. The formation of a series of (5,5)-, (5,6)-, (6,5)-, and (6,6)-fused bicyclic ring systems was systematically studied by implementation of a common strategy involving *N*-acyliminium intermediates. These are highly reactive and transformed further in intramolecular cascade reactions with strong as well as weak *C*, *N*, *S*, and *O*-nucleophiles. The methodology was successfully applied to the conversion of peptidomimetics into constrained small molecule core structures, such as the hexahydropyrrolo[2,1-*b*][1,3]oxazines, generally with full control of diastereoselectivity (>20:1) and in purities above 90%.

Introduction

Solid-phase synthesis, originally developed for peptide assembly, has become a powerful tool for the construction of peptidomimetics, and even small molecules.[1–3] Following the pioneering work of Merrifield,[4] advances in supports, protecting group strategies, and extensive optimization of chemical methodology have expanded the scope of solid-phase chemistry from mere peptide synthesis to the efficient generation of pharmacologically relevant small heterocyclic molecules, such as pyrazines, benzodiazepines, hydantoins, and triazoles,[5–11] and the total synthesis of natural products and their analogues.[12–23] Particularly the recent focus on quantitative chemical transformations or "click-chemistries"[24] has been driving the development of supported parallel and combinatorial synthesis.

Simultaneously, the advent of high-throughput assays for biological testing of chemical entities has created a need for larger and more diverse compound collections and molecular libraries. This need can most conveniently be met by following a combinatorial approach, which is inherently linked to solid-phase synthesis, thus stimulating continuous development of chemistries compatible with solid supports. Although peptide libraries may routinely be generated on the solid support, the associated poor pharmacokinetic properties of peptides has generally limited their development into drugs. Approaches that take advantage of well-established solid-phase peptide synthesis protocols and address the issues of pharmacokinetics and optimized pharmacophoric display have been realized through the field of peptidomimetics.[25–27] Particularly the design and synthesis of small heterocyclic core structures continues to be an important area of research in combinatorial chemistry.[28]

N-Acyliminium ions are versatile intermediates for the generation of small heterocyclic molecules.[29–31] Their reaction with various nucleophilic moieties, e.g., in amidoalkylations, and Mannich-type condensation reactions, represent well-known approaches toward medicinally important ring systems, such as tetrahydroisoquinolines and tetrahydro-β-carbolines. Toward this end, the Pictet–Spengler cascade reaction,[32,33] i.e., the intramolecular reaction of iminium intermediates with aromatic π-nucleophiles, continues to be widely explored in solution-phase[34–37] and solid-phase synthesis.[33,38] Our group has been interested in solid-phase variants of the Pictet–Spengler reaction as rich sources for the generation of combinatorial libraries.[33,39–43] An important finding in these studies was the propensity of peptide aldehydes to undergo intramolecular condensation reactions for the generation of cyclic *N*-acyliminium intermediates, which underwent intramolecular Pictet–Spengler type cyclization reactions with neighboring aromatic moieties (Scheme 1). The aldehyde functionality may be generated quantitatively by either acidic cleavage of *N*,*O*-acetals,[44,45] or by oxidative cleavage of olefins.[41] More recently, our preliminary results indicated that the solid-phase chemistry of *N*-acyliminium intermediates could be generally extended to most heteroatom-nucleophilic cyclization reactions, thereby generating a range of (5,5)-, (5,6)-, and (5,7)-fused aza-, thia-, and oxabicycloalkanes.[39]

In the present investigation, we wish to report the scope and applicability of various cyclic *N*-acyliminium intermediates, specifically for the generation of *new combinations of ring sizes and ring systems*, using different nucleophilic moieties and aldehyde precursors. Bearing in mind the previous generation of (5,5)-, (5,6)-, and (5,7)-fused scaffolds,[33,39–43] we decided to investigate diversity expansion to the corresponding (6,5)-, (6,6)-, (6,7)-, (7,5)-, (7,6)-, and (7,7)-ring systems, requiring new chemistry as well as novel sets of building blocks.

The synthesis strategy involves the coupling of a selection of masked aldehyde building blocks to the *N*-terminal of solid-supported peptides (Fig. 1, **7**). Once liberated, the aldehydes **8** condense with the amide backbone to generate hydroxylactams **9** of various ring sizes. Upon addition of acid, the equilibrium is shifted toward *N*-acyliminium ion

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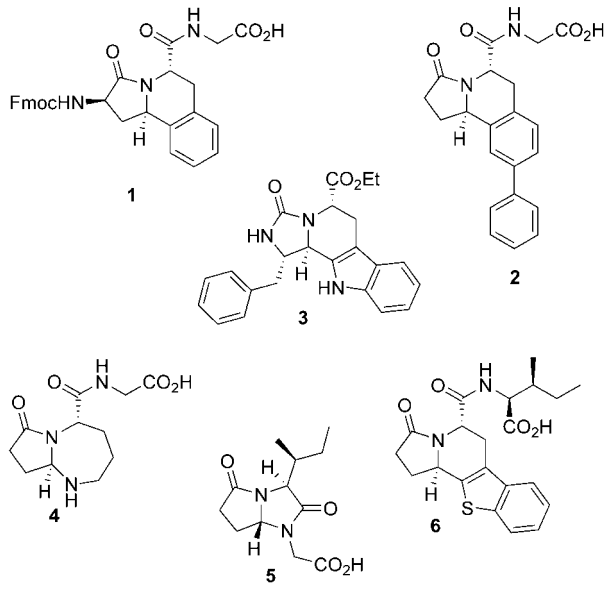
10.1021/cc700097k CCC: $37.00
Published on Web 11/12/2007

Scheme 1. Heterocycles Accessible via Solid-Supported *N*-Acyliminium Intermediates[39–43]



intermediates **10**, which may be trapped intramolecularly by nucleophilic moities (*C*- or heteroatom-based nucleophiles), conveniently positioned in the vicinity of the reactive center by the architecture of the molecular framework. Overall, this reaction cascade results in bicyclic structure **11** attached to a peptide sequence that may easily be cleaved from the solid support by cleavage of a base labile linker.

Results and Discussion

The *N*-acyliminium ion mediated cascade reaction was in the present study successfully applied to the construction of different fused ring systems. Notably, novel (5,6)-fused ring systems were successfully synthesized as illustrated by the synthesis of a constrained enkephalin analogue and the generation of a range of isoindolinones. Furthermore, the present study focuses on the extension of the strategy to larger ring-systems. To our delight, the generation of (6,6)-fused ring systems appears to be of general applicability. In addition, new ways of generating aldehydes on solid phase by means of oxidative cleavage of olefins or oxidation of alcohols were investigated and were in a number of cases shown to be equally as effective as the previously studied acid-labile *N*,*O*-acetals. The construction of masked peptide aldehydes on solid phase and their subsequent collapse into constrained heterocyclic structures by a series of cascade reactions takes advantage of a highly favorable entropy component in intramolecular reactions and thus appears to be a powerful tool for the generation of pharmacologically interesting small molecules with high stereoselectivity. The requirement for a significant entropy contribution is also expected to limit the chemistry to structures allowing a suitable arrangement of functional groups during the transition state of the reaction.

The chemistry was developed for synthesis on solid support and all solid-phase transformations were carried out using the amino-functionalized $PEGA_{800}$ resin.[46] The base-labile hydroxymethyl-benzoic acid (HMBA) linker was coupled to the resin ($PEGA_{800}$) via an *N*-[1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide (TBTU) activation procedure,[47] followed by 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT)-mediated ester bond formation[48] to attach the first amino acid residue (glycine). Subsequent cycles of Fmoc-deprotection and TBTU-mediated coupling reactions provided in all cases peptidic aldehyde precursors in excellent purities (>95%) (Scheme 2). All compounds were released from the solid support by basic hydrolysis with 0.1 M NaOH (aq) and neutralized with 0.1 M HCl (aq). Corrected for the salt contents, crude yields for all products arising from solid-phase transformations were typically around 70–90%. When purified by preparative RP-HPLC, the yields of desalted, purified products generally dropped to 45–85%.

Synthesis of Constrained Enkephalin Analogue 15. In recent years, tremendous efforts have been aimed at the introduction of structural constraints in synthetic peptide chains with the purpose of mimicking secondary structural elements believed to be critical for receptor recognition.[49,50] In this context, it was decided to explore a recently developed protocol for the solid-phase oxidative cleavage of olefins.[41] We have previously shown that the oxidative cleavage of allylglycine derivatives could serve as a route to aldehydes capable of undergoing intramolecular condensation reactions. The amino functionality of the resulting bicyclic heterocycles has the potential to extend the peptide chain, thereby effectively inducing a structural constraint at the center of the bioactive molecule. Although such constraint-inducing bicyclic motifs are well-known,[25] few have dealt with their *de novo* synthesis on the solid support.[51,52] Initially, the approach was verified by using the homoserine side-chain of **12** as an *O*-nucleophile. Pleasingly, by subjecting **12** to OsO_4/$NaIO_4$/1,4-diazabicyclo[2.2.2]octane (DABCO)-medi-

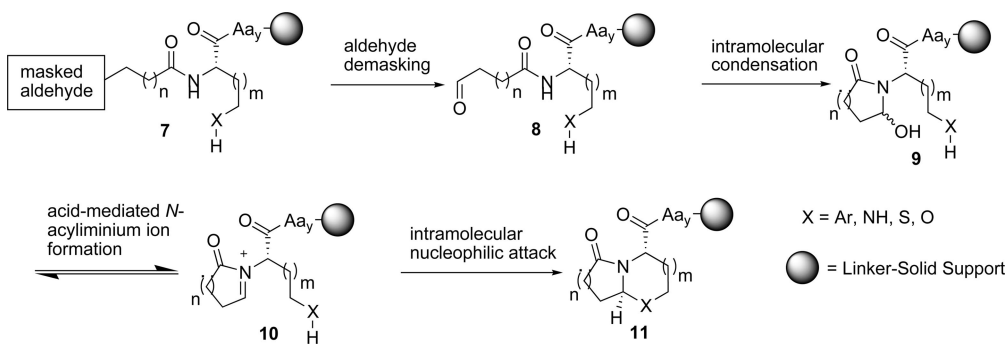
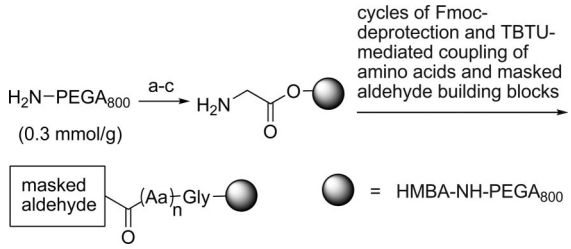


Figure 1. The intramolecular *N*-acyliminium cascade reaction used for the synthesis of fused bicyclic ring systems.

Scheme 2. Solid-Phase Synthesis of Masked Aldehydes (Reagents and conditions: (a) HMBA, TBTU, NEM, DMF; (b) Fmoc-Gly-OH, MSNT, 1-methylimidazole, CH_2Cl_2; (c) 20% piperidine (DMF))



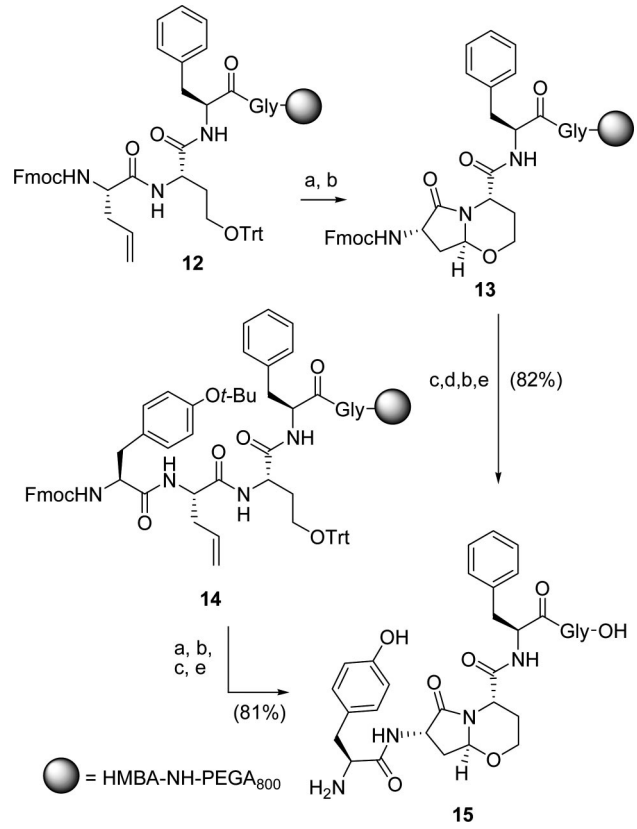
ated oxidative cleavage conditions, followed by treatment with aqueous TFA and subsequent treatment with dry 50% TFA (CH_2Cl_2), the desired bicyclic hexahydro-pyrrolo[2,1-*b*][1,3]oxazine **13** was obtained in excellent purity and diastereoselectivity (both >90%). Subsequent derivatization of the protected amino-functionalized bicyclic ring system was illustrated by installing a tyrosine residue, thus forming enkephalin analogue **15** with a constrained core previously suggested by Hruby and co-workers.[52] Changing the order of events, compound **15** was also generated by first carrying out the peptide synthesis, then the oxidative cleavage followed by the subsequent cascade reaction. However, both strategies proved to work equally well, providing the target compound in purities exceeding 80% (Scheme 3).

The purified peptide was subjected to conformational analysis by NOESY and in addition to the sequential NOEs expected for the molecule from its relatively rigid backbone, strong NOEs were observed between the two aromatic protons of the tyrosine and those of phenylalanine. This NOE confirmed the structure determined by nonconstrained molecular dynamics in aqueous solution for 50 ps at 500 K, then 300 ps at 400 K. The result of the dynamics simulation is presented in the form of 30 low energy conformations from the 300 ps simulation in figure 2.

OsO_4/$NaIO_4$/DABCO-Mediated Oxidative Cleavage of 2-Vinylbenzamide Derivatives: Synthesis of Isoindolinones. Isoindolinones constitute important core structures of naturally occurring complex alkaloids and are of significant interest due to a multitude of reported biological activities.[53–58] Bearing in mind approaches to isoindolinones using *N*-acyliminium ion intermediates,[59,60] we envisioned the use of 2-vinylbenzoic acid as a suitable masked aldehyde building block. By subjecting 2-vinylbenzamide derivatives to OsO_4/$NaIO_4$/DABCO-mediated oxidative cleavage, followed by acid-mediated *N*-acyliminium cyclization reactions, isoindolinone core structures should be readily accessible on the solid phase. 2-Vinylbenzoic acid was conveniently synthesized from 2-carboxybenzaldehyde by Wittig reaction with KO*t*-Bu/$MePh_3PBr$ in excellent yield (95%). The building block was cleanly attached to the *N*-terminal of various peptide residues, containing amino acids with diverse nucleophilic side-chains, using the TBTU-activation procedure.

Amino acid residues containing *C*-nucleophiles, i.e. tryptophan, phenylalanine, (3,4-dimethoxyphenyl)alanine, (2-thienyl)alanine, (3-benzothienyl)alanine, and (2-furyl)alanine, as well as heteroatom-based nucleophiles (protected), i.e. threonine (*t*-Bu), homoserine (Trt), ornithine (Boc), aspar-

Scheme 3. Synthesis of Constrained Peptide **15** by Use of *N*-Acyliminium Intermediates (Product Purities Were Determined by RP-HPLC)(Reagents and Conditions: (a) OsO_4, $NaIO_4$, DABCO, THF/H_2O (1:1); (b) 10% TFA (aq), then 50% TFA (CH_2Cl_2); (c) 20% piperidine (DMF); (d) Fmoc-Tyr(O*t*-Bu)-OH, TBTU, NEM, DMF; (e) 0.1 M NaOH (aq))



agine (Trt), and diaminopropionic acid (Boc), were investigated. Except for the Trp-derivative, presumably due to oxidation of the indole moiety, all compounds underwent clean oxidative cleavage, as demonstrated by LCMS analysis of the resulting aldehydes/hydroxylactams. However, when subjected to acidic reaction conditions (50% TFA in CH_2Cl_2) only compounds **16–18** were converted cleanly to the corresponding isoindolinones **19–21** in excellent purities (Scheme 4). All other cyclization attempts resulted in complex product mixtures, difficult to separate. The stereochemistry of compounds **19–21** was assigned by NOE experiments. A strong NOE relationship was observed

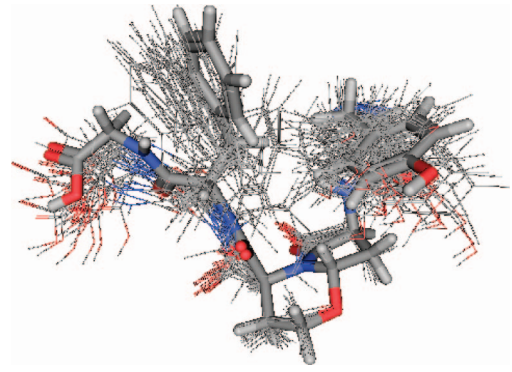
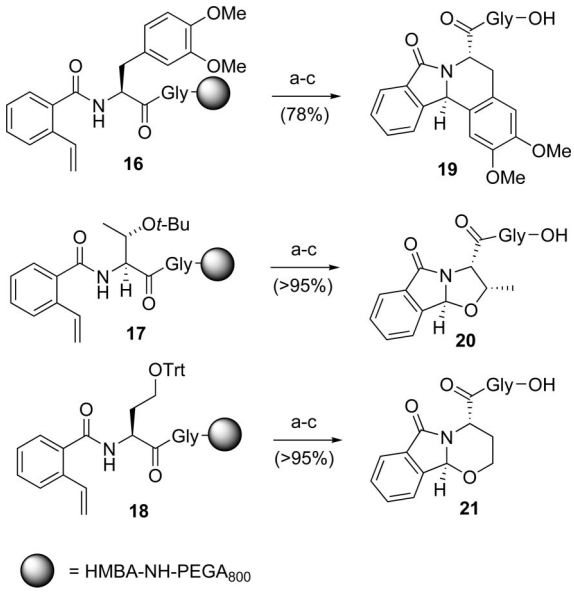


Figure 2. Conformational ensemble of 30 low energy conformations of enkephalin analogue **15**.

Scheme 4. Solid-Phase Synthesis of Isoindolinones (Product Purities Were Determined by RP-HPLC)(Reagents and Conditions: (a) OsO_4/$NaIO_4$/DABCO, THF/H_2O (1:1); (b) 50% TFA (CH_2Cl_2); (c) 0.1 M NaOH (aq))



between the amide proton of the glycine residue and the proton on the newly formed stereogenic center.

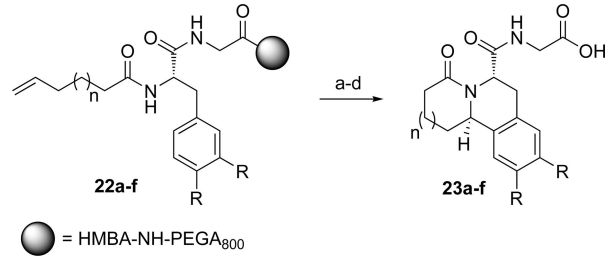
Construction of Novel (5,6)- and (6,6)-Fused Ring Systems. Having established the potential of the strategy for the synthesis of (5,5)- and (5,6)-fused ring systems derived from cyclic 5-membered *N*-acyliminium intermediates, it was decided to explore whether the methodology could be extended to 6- and 7-membered hydroxylactams/*N*-acyliminium intermediates. By using the 1- and 2-carbon higher homologues of previously reported masked aldehyde building blocks,[44] a comparative study of alkenes, alcohols, and *N*(Boc)-1,3-oxazinanes as aldehyde precursors in the synthesis of these (6,6)- and (7,6)-fused ring systems was executed.

Oxidative Cleavage of Alkenes. Although limited by oxidation-sensitive residues, the alkene oxidation strategy is attractive since a range of terminal enoic acids are commercially available, e.g. 4-pentenoic acid, 5-hexenoic acid, and 6-heptenoic acid. Having coupled these building blocks to two phenylalanine derivatives, the resulting substrates **22a-f** were subjected to the synthetic steps of oxidative cleavage and acidic treatment (Table 1). Pyrroloisoquinolinones **23a** and **23d** (entries 1 and 4) were obtained in excellent purities (>95%), while (6,6)-fused pyridoisoquinolines **23b** and **23e** could only be obtained in intermediate purities (entries 2 and 5). The (7,6)-fused ring systems **23c** and **23f** could not be detected as reaction products by MS of the reaction mixtures (entries 3 and 6).

Oxidation of Alcohols. Considering the less than quantitative formation of the (6,6)-fused ring systems to provide satisfying purities, primary alcohols were investigated as aldehyde precursors. For this purpose, suitable TBDMS-protected building blocks **30**–**32** were readily prepared from the corresponding diols via monosilylation and subsequent TEMPO-oxidation (Scheme 5).

These were attached to three different solid-supported peptide residues, containing phenylalanine, (3,4-dimethoxyphenyl)alanine, and tryptophan, respectively. Following a clean desilylation using TBAF/AcOH (THF), the resulting solid-supported alcohols were then subjected to Dess–Martin periodinane oxidation conditions (Table 2). The (5,6)-fused Pictet–Spengler products **23a**, **23d**, and **45** (entries 1, 4. and 7) could easily be accessed, thus providing an unprecedented rapid pathway for accessing pyrroloisoquinolines and indolizinoindoles on the solid phase. The ease with which the TBDMS-protected building blocks are synthesized offers an advantage to the lengthier synthesis of *N*(Boc)-1,3-oxazinane analogues. However, the shortcomings of the strategy are illustrated by the difficulties now encountered in the synthesis of (6,6)- and (7,6)-fused ring system. As also noted in the oxidative cleavage approach (Table 1), the products resulting from the reaction of the intermediate 6-membered hydroxylactams could only be obtained in modest purities (entries 2 and 5), and 7-membered hydroxylactams failed to undergo the desired cyclization process (entries 3 and 6).

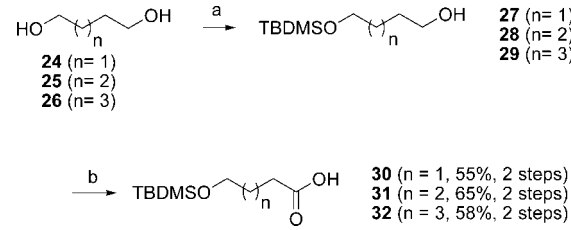
Table 1. Solid-Phase Intramolecular *N*-Acyliminium Pictet–Spengler Reactions Using Alkenes As Aldehyde Precursors[a]



entry	alkene	R	n	product[b], purity (%)
1	**22a**	H	0	**23a**, >95
2	**22b**	H	1	**23b**, 76
3	**22c**	H	2	**23c**, 0
4	**22d**	OMe	0	**23d**, >95
5	**22e**	OMe	1	**23e**, 66
6	**22f**	OMe	2	**23f**, 0

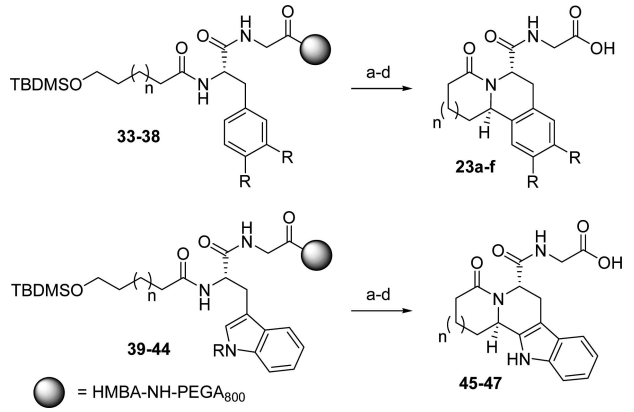
[a] Reagents and conditions: (a) OsO_4/$NaIO_4$/DABCO, THF/H_2O (1:1); (b) 10% TFA (aq); (c) 50% TFA (CH_2Cl_2); (d) 0.1 M NaOH (aq). [b] All peptides were analyzed by RP-HPLC after oxidative cleavage, which showed complete conversion of the starting compounds and formation of the aldehyde/hydroxylactam in all cases as indicated by MS.

Scheme 5. Synthesis of TBDMS-Protected Alcohols **23**–**25** (Reagents and Conditions: (a) TBDMSCl, Imidazole, DMF; (b) TEMPO, TBABr, NaBr, NaOCl, $NaHCO_3$, CH_2Cl_2)



Acidic Hydrolysis of *N*,*O*-Acetals. Previous investigations have established acid labile *N*(Boc)-1,3-oxazinanes as convenient aldehyde precursors in the synthesis of 5-membered fused bicyclic lactams.[39] Consequently, we speculated if the 1- and 2-carbon higher homologues could be more successful for the generation of larger cyclic *N*-acyliminium intermediates, i.e., the 6- and 7-membered entities. Swern oxidation of alcohols **28** and **29**, and subsequent *N*(Boc),*O*-acetalization of the resulting aldehydes **48** and **49**, afforded protected derivatives **50** and **51**. Desilylation using TBAF, followed

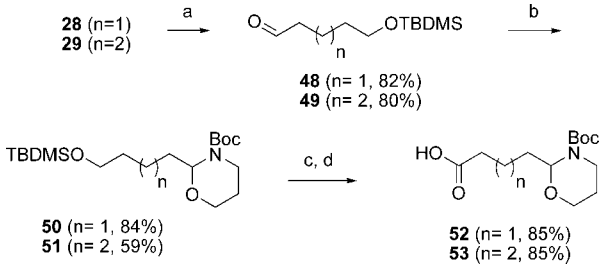
Table 2. Solid-Phase Intramolecular *N*-Acyliminium Pictet–Spengler Reactions Using Silylethers As Aldehyde Precursors[a]



entry	silylether	R	n	product, purity (%)
1	**33**	H	0	**23a**, 86
2	**34**	H	1	**23b**, 43
3	**35**	H	2	**23c**, 0
4	**36**	OMe	0	**23d**, 89
5	**37**	OMe	1	**23e**, 47
6	**38**	OMe	2	**23f**, 0
7	**39/42**	H/Boc	0	**45**, 93
8	**40/43**	H/Boc	1	**46**, 0[b]
9	**41/44**	H/Boc	2	**47**, 0[b]

[a] Reagents and conditions: (a) TBAF, AcOH, THF; (b) Dess–Martin periodinane, CH_2Cl_2; (c) 10% TFA (aq); (d) 50% TFA (CH_2Cl_2); (e) 0.1 M NaOH (aq). [b] Decomposition of the peptide was observed.

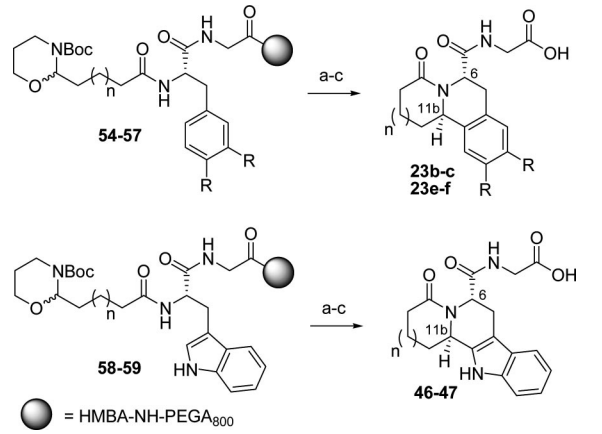
Scheme 6. Synthesis of *N*(Boc)-1,3-Oxazinanes **52** and **53** (Reagents and Conditions: (a) Oxalyl Chloride, DMSO, Et_3N, CH_2Cl_2; (b) $NH_2(CH_2)_3OH$, Na_2SO_4, Boc_2O, Toluene; (c) TBAF, THF; (d) TEMPO, TBABr, NaBr, NaOCl, $NaHCO_3$, CH_2Cl_2)



by TEMPO-oxidation of the primary alcohols gave the carboxylic acid building blocks **52** and **53** in good overall yields (Scheme 6). These compounds were, however, unstable upon prolonged storage in the freezer (decomposition to the aldehyde was generally observed), presumably due to aldehyde demasking mediated by the carboxylic acid functionality.[61]

With building blocks **52** and **53** in hand, their cascade reaction with three *C*-nucleophiles, i.e., the aromatic side chains of phenylalanine, (3,4-dimethoxyphenyl)alanine and tryptophan, was examined (Table 3). To our delight, we were for the first time able to obtain the desired hexahydro-2*H*-pyrido[2,1-*a*]isoquinolines **23b** and **23e** in excellent purities (entries 1 and 3). However, no traces of the corresponding products **23c** and **23f** resulting from reaction with 7-membered *N*-acyliminium internediates were detected (entries 2 and 4). The diastereoselectivity of the reactions toward **23b** and **23e** was excellent (>20:1).[62] Curiously, there was no

Table 3. Solid-Phase Intramolecular *N*-Acyliminium Pictet–Spengler Reactions Using *N*,*O*-Acetals As Aldehyde Precursors[a,b]



entry	*N*,*O*-acetal	R	n	product[c], purity (%)
1	**54**	H	1	**23b**, >95
2	**55**	H	2	**23c**, 0
3	**56**	OMe	1	**23e**, >95
4	**57**	OMe	2	**23f**, 0
5	**58**	-	1	**46**, 0[d]
6	**59**	-	2	**47**, 0[d]

[a] Reagents and conditions: (a) 10% TFA (aq); (b) 50% TFA (CH_2Cl_2); (c) 0.1 M NaOH (aq). [b] The use of phenylglycine and homophenylalanine combined with the building blocks **52** and **53** was also attempted, albeit none of the desired products were obtained. [c] HPLC and MS indicated complete conversion to the aldehydes/hydroxylactams. [d] Decomposition of the peptide was observed.

success of tryptophan derivatives to provide compounds **46** and **47** (entries 5 and 6). On the other hand, a series of other aromatic heterocycles proved highly efficient in this context (Scheme 7), giving the tri- and tetracyclic compounds **64–67** in excellent purities.

Having established the feasibility of forming pyridoisoquinoline ring systems, heteroatom-based amino acid side-chain nucleophiles were investigated in the reaction with 6-membered *N*-acyliminium intermediates (Table 4). Gratifyingly, the desired products **75–79** and **81** with (6,5)- and (6,6)-bicyclic core structures were obtained in excellent purities. Notably, *N*, *O*, and *S*-based nucleophiles were applicable.

To devise future explorations of the appendage potential of these new scaffolds, building block **84**, containing an amino handle for further derivatization, was prepared. The building block was synthesized from the known tribenzylated aldehyde **82**,[63] prepared according to the method of Taddei from commercially available glutamic acid. Compound **82** was subjected to the *N*(Boc),*O*-acetalization procedure to afford **83**, which was hydrolyzed using KOH in ethanol to give the desired carboxylic acid **84** (Scheme 8).

The building block **84** was then attached to two different peptides, each containing a different nucleophilic moiety, i.e., the electron-rich benzene ring of **85**, and the hydroxy functional group of **86**. Subjecting the compounds to acidic treatment provided hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline **87** and hexahydro-pyrido[2,1-*b*][1,3]oxazine **88** in satisfying purities (84%, and 78%, respectively), thus demonstrating

Scheme 7. Solid-Phase Intramolecular *N*-Acyliminium Pictet–Spengler Reactions for the Synthesis of (6,6)-Fused Heterocyclic Ring-Systems (Product Purities Were Determined by RP-HPLC) (Reagents and Conditions: (a) 10% TFA (aq); (b) 50% TFA (CH_2Cl_2); (c) 0.1 M NaOH (aq))

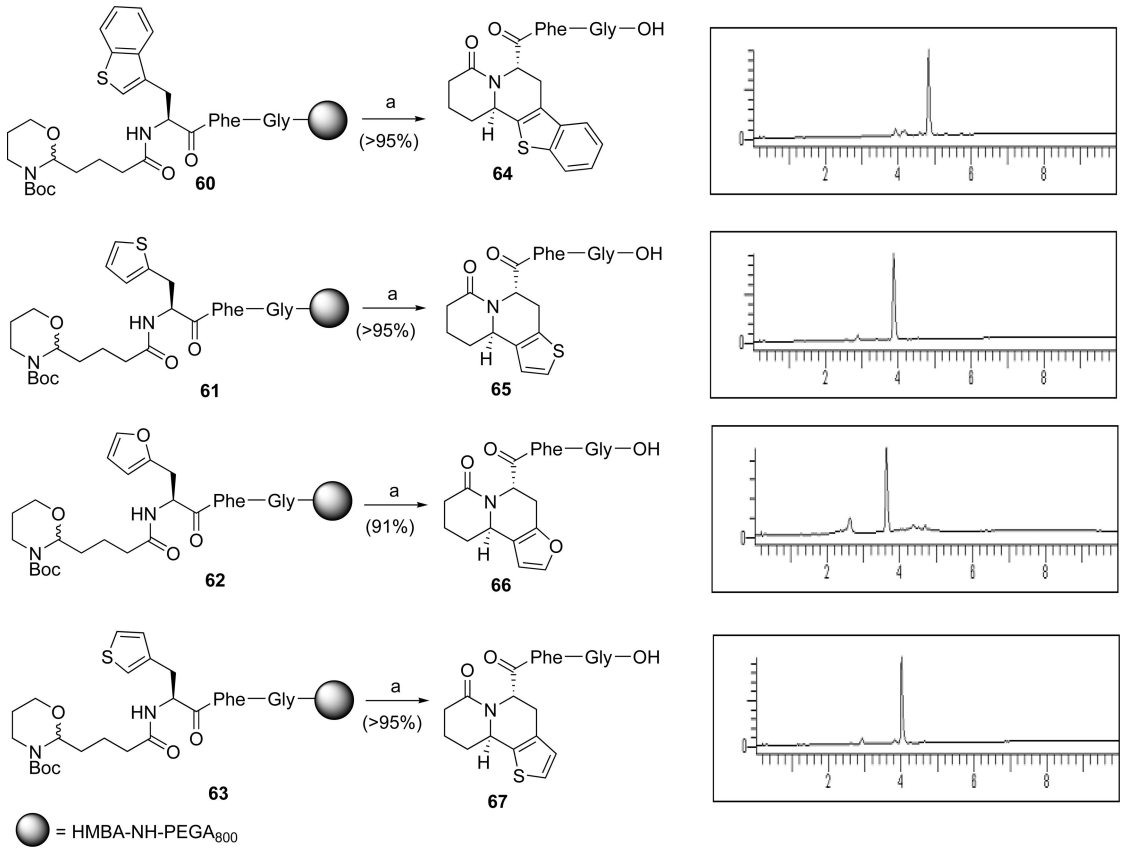
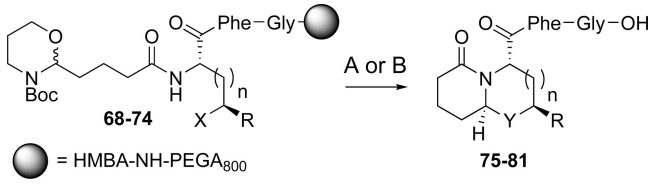


Table 4. Solid-Phase Synthesis of (6,5)- and (6,6)-Oxa-, Aza-, and Thiabicycloalkanes



entry	*N,O*-acetal	X	R	Y	n	reaction conditions[a]	product, purity (%)
1	**68**	O*t*-Bu	H	O	0	B	**75**, >95
2	**69**	O*t*-Bu	Me	O	0	A or B	**76**, >95
3	**70**	OTrt	H	O	1	A or B	**77**, >95
4	**71**	NHBoc	H	NBoc	0	A	**78**, >95
5	**72**	NHBoc	H	NBoc	1	A	**79**, 86
6	**73**	NHBoc	H	NBoc/NH	2	A/B	**80**, 0
7	**74**	STrt	H	S	0	A or B	**81**, >95

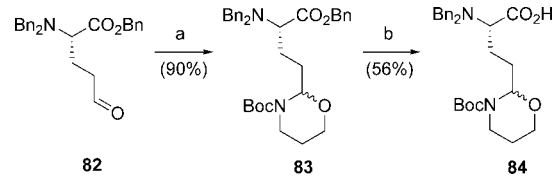
[a] Conditions A: (a) 10% TFA (aq); (b) 0.1 M NaOH (aq). Conditions B: (a) 10% TFA (aq); (b) 50% TFA (CH_2Cl_2); (c) 0.1 M NaOH (aq).

the applicability of this building block for the general access to (6,6)-fused ring systems (Scheme 9).

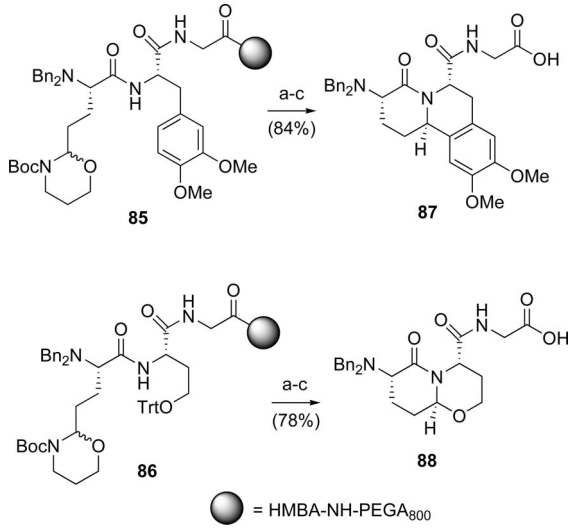
Conclusions

The present study emphasizes the power of *N*-acyliminium intermediates for use in cascade reactions leading to complex heterocyclic scaffolds on the solid phase. The strategy entails the intramolecular positioning of all functional groups, i.e., aldehyde, amine, and nucleophile, prior to the acid-mediated cascade process. Substrates are rapidly constructed on the solid support. The strategy is highly versatile, as illustrated for the synthesis of a multitude of different ring systems, ranging from isoindolinone scaffolds to the synthesis of pyridoisoquinolines. The compounds are usually obtained in excellent purities, with high diastereomeric control. A range of fused (5,6)-, (6,5)-, and (6,6)-ring systems have been synthesized on solid phase. Despite the success of comparable solution-phase reactions,[29] the indole moiety of tryptophan residues could not be made to react with 6-membered *N*-acyliminium intermediates. Access to the structurally interesting hexahydroindoloquinolizinones is therefore not yet within the scope of the methodology. Similarly, 7-membered *N*-acyliminium intermediates, known to be reactive toward various nucleophilic groups in solution-phase chemistry,[31] failed to cyclize and underwent instead drastic decomposition on the solid support. However, there is no doubt that the range of structures presented herein merely represent a small fraction of the accessible heterocyclic structures on solid phase using *N*-acyliminium ion chemistry.

Scheme 8. Synthesis of Glutamic Acid Derived *N*(Boc)-1,3-Oxazinane Building Block (Reagents and Conditions: (a) $NH_2(CH_2)_3OH$, Na_2SO_4, Boc_2O, Toluene; (b) KOH, EtOH)



Scheme 9. Use of Glutamic Acid Derived Building Block **84** with Various Nucleophiles (Product Purities Were Determined by RP-HPLC) (Reagents and Conditions: (a) 10% TFA (aq); (b) 50% TFA (CH_2Cl_2); (c) 0.1 M NaOH (aq))



Current work in our group focuses on the generation of combinatorial and parallel libraries of small molecules using the presented strategy and will be reported in due course.

Experimental Section

General Methods. General methods are reported in the Supporting Information.

Solid-Phase Procedures. Attachment of the 4-hydroxymethylbenzoic acid (HMBA) linker to the amino-functionalized resin was carried out by premixing 4-hydroxymethylbenzoic acid (HMBA, 3.0 equiv), *N*-ethylmorpholine (NEM, 4.0 equiv), and *N*-[1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide (TBTU, 2.88 equiv) for 5 min in DMF. The resulting solution was added to DMF preswollen resin and allowed to react for 2 h, followed by washing with DMF (6×), and CH_2Cl_2 (6×). Coupling of the first amino acid (Gly) to the HMBA-derivatized resin was acccomplished by treating the freshly lyophilized resin with a mixture of the Fmoc-Gly OH (3.0 equiv), 1-methylimidazole (MeIm, 2.25 equiv), and 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT, 3.0 equiv) in CH_2Cl_2/THF (20:1). The coupling was repeated once. Peptide synthesis and attachment of the different building blocks to the amino-functionalized resin were subsequently accomplished following standard amino acid coupling procedures (Fmoc-Aa-OH, TBTU, NEM, DMF) as described above for the attachment of the HMBA linker. The usual washing protocol followed each coupling and deprotection step. Completion of the reaction was monitored using the Kaiser test. Fmoc-deprotection was accomplished with 20% piperidine in DMF, first for 2 min, and then for 18 min, followed by washing with DMF (6×).

The oxidative cleavage of solid-phase peptide olefins was carried out by addition of $NaIO_4$ (10.0 equiv) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 5.0 equiv) to the resin preswollen in THF/water (1:1). Thereafter OsO_4 (0.05 equiv, 2.5 wt. % solution in 2-methyl-2-propanol) was added. The initially vaguely reddish solution reaction mixture was shaken overnight at rt. Subsequently the resin was washed with water (6×), 10% TFA (aq) (3×), water (6×), DMF (6×), and CH_2Cl_2 (6×) in a plastic syringe fitted with a teflon filter.

The solid-phase cleavage of silylethers was carried out by addition of tetrabutylammonium fluoride (TBAF, 4 equiv, 1.0 M solution in THF) buffered with AcOH (4.5 equiv), to the resin preswollen in THF. The reaction was left for 2 h at rt, by which time the resin was washed with THF (3×), water (6×), DMF (6×), and CH_2Cl_2 (6×).

The solid-phase oxidation of peptide alcohols was carried out by addition of Dess–Martin periodinane (DMP, 6 equiv) to the resin preswollen in CH_2Cl_2/MeCN (1:1). The reaction mixture was shaken overnight at rt. Subsequently the resin was washed with MeCN (3×), 10% $Na_2S_2O_3$ (aq) (4×), water (3×), DMF (6×), and CH_2Cl_2 (6×).

Building Block Synthesis. 2-Vinylbenzoic Acid. A solution of potassium *tert*-butoxide (205 mmol, 23.0 g) in THF (100 mL) was added dropwise to a solution of methyltriphenylphosphonium bromide (140 mmol, 50.0 g) in THF (200 mL) at rt. The reaction mixture was stirred for 90 min, before dropwise addition of 2-carboxybenzaldehyde (87 mmol, 13.0 g). When the addition was complete, the reaction temperature was raised to 60 °C and stirring was continued overnight. After addition of acetic acid (5 mL), the reaction mixture was filtered through a pad of celite and concentrated by rotary evaporation. The residue was taken up in ethyl acetate and washed thoroughly with sat. $NaHCO_3$ (aq). The combined aqueous washings were acidified with 1.0 M HCl (aq), then back-extracted with ethyl acetate. The organic layer was washed with water and brine, then dried over $MgSO_4$, filtered, and rotary evaporated to provide the pure title compound as a white solid (12.25 g, 95%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 13.01 (bs, 1H), 7.79 (dd, 1H, $J = 1.3$ Hz, $J = 7.8$ Hz), 7.67 (d, 1H, $J = 7.8$ Hz), 7.53 (dt, 1H, $J = 1.4$ Hz, $J = 7.6$ Hz), 7.42 (dd, 1H, $J = 10.9$ Hz, $J = 17.6$ Hz), 7.38 (dt, 1H, $J = 1.3$ Hz, $J = 7.5$ Hz), 5.74 (dd, 1H, $J = 1.3$ Hz, $J = 17.6$ Hz), 5.33 (dd, 1H, $J = 1.3$ Hz, $J = 11.0$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 168.4, 137.7, 135.1, 131.6, 129.8, 129.6, 127.5, 126.3, 116.2. MS (ES) calcd for $C_9H_7O_2$ $[M - H]^-$ 147.0, found 147.0.

4-(*tert*-Butyl-dimethyl-silanyloxy)-butan-1-ol (27). General Procedure (I): Monosilylation of Diols. *tert*-Butyldimethylsilyl chloride (4.18 g, 27.7 mmol) and imidazole (7.55 g, 111 mmol) weredissolved in *N,N*-dimethylformamide (100 mL). 1,4-Butanediol (10.0 g, 111 mmol) was added dropwise and the resultant solution was stirred overnight. Water (100 mL) and petroleum ether (200 mL) were added, and the organic phase was separated. The aqueous phase was further extracted with petroleum ether (2 × 200 mL). The combined organics were dried over sodium sulfate. The solvent was removed by rotary evaporation and the resulting oil was subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate, 8:2) to give the title compound as a colorless oil (4.43 g, 78%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.68–3.61 (m, 4H), 1.68–1.60 (m, 4H), 0.90 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 63.2, 62.4, 29.8, 29.6, 25.8, 18.1, −5.4.

5-(*tert*-Butyl-dimethyl-silanyloxy)-pentan-1-ol (28). Following general procedure (I) the reaction of *tert*-butyldimethylsilyl chloride (9.05 g, 60.01 mmol), imidazole (16.34 g, 240 mmol), and 1,5-pentanediol (25.0 g, 240 mmol) gave after flash column chromatography on silica gel (petroleum ether/ethyl acetate, 8:2) the title compound as a colorless oil (11.08 g, 85%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.63 (q, 4H, J = 6.5 Hz), 1.49 (m, 7H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 63.1, 62.4, 32.4, 32.3, 25.9, 21.9, 18.2, −5.4.

6-(*tert*-Butyl-dimethyl-silanyloxy)-hexan-1-ol (29). Following general procedure (I) the reaction of *tert*-butyldimethylsilyl chloride (3.20 g, 21.2 mmol), imidazole (5.76 g, 84.6 mmol), and 1,6-hexanediol (10.0 g, 84.6 mmol) gave after flash column chromatography on silica gel (petroleum ether/ethyl acetate, 8:2) the title compound as a colorless oil (3.1 g, 63%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.64 (t, 2H, J = 6.6 Hz), 3.60 (t, 2H, J = 6.5 Hz), 1.60–1.47 (m, 4H), 1.44–1.33 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 63.1, 62.6, 32.7, 32.6, 25.8, 25.5, 25.4, 18.2, −5.3.

4-(*tert*-Butyl-dimethyl-silanyloxy)-butyric acid (30).[64] **General procedure (II): TEMPO Oxidation of Alcohols To Carboxylic Acids.** To a 0 °C cold solution of **27** (500 mg, 2.45 mmol) in CH_2Cl_2 (50 mL) was added 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (15 mg, 0.10 mmol) followed by a mixture of NaBr (38 mg, 0.37 mmol), tetrabutylammonium bromide (TBABr) (39 mg, 0.12 mmol), water (8 mL), $NaHCO_3$ sat. (aq) (16 mL), and NaOCl (1.3 M (aq), 5.6 mL, 7.34 mmol). The mixture was stirred vigorously at 0 °C for 2 h, quenched with MeOH (5 mL), acidified to pH 4 with 1.0 M HCl (aq), and extracted with ethyl acetate (3 × 75 mL). The combined extracts were dried over Na_2SO_4 and concentrated to an oil which was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 8:2), affording the title compound as a colorless oil (373 mg, 70%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.67 (t, 2H, J = 6.0 Hz), 2.45 (t, 2H, J = 7.3 Hz), 1.85 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 179.9, 61.93 30.7, 27.6, 25.8, 18.2, −5.5.

5-(*tert*-Butyl-dimethyl-silanyloxy)-pentanoic acid (31).[65] Following general procedure (II) the reaction of TEMPO (20 mg, 0.13 mmol), NaBr (49 mg, 0.48 mmol), TBABr (52 mg, 0.16 mmol), NaOCl (7.4 mL, 9.62 mmol), $NaHCO_3$ (aq) (21.2 mL), and **28** (700 mg, 3.21 mmol) gave after flash column chromatography on silica gel (petroleum ether/ethyl acetate, 8:2) the title compound as a colorless oil (567 mg, 76%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.63 (t, 2H, J = 6.1 Hz), 2.38 (t, 2H, J = 7.3 Hz), 1.76–1.51 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR(62.5 MHz, $CDCl_3$): δ 179.9, 62.6, 33.7, 31.9, 25.9, 21.2, 18.3, −5.3.

6-(*tert*-Butyl-dimethyl-silanyloxy)-hexanoic acid (32).[66] Following general procedure (II) the reaction of TEMPO (19 mg, 0.12 mmol), NaBr (47 mg, 0.45 mmol), TBABr (49 mg, 0.15 mmol), NaOCl (7 mL, 9.03 mmol), $NaHCO_3$ (aq) (19.9 mL), and **29** (700 mg, 3.01 mmol) gave after flash column chromatography on silica gel (petroleum ether/ethyl acetate, 8:2) the title compound as a colorless oil (684 mg, 92%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.61 (t, 2H, J = 6.3 Hz), 2.36 (t, 2H, J = 7.5 Hz), 1.72–1.35 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 179.9, 62.8, 35.2, 34.0, 32.3, 25.9, 25.3, 24.4, 18.3, −5.3.

5-(*tert*-Butyl-dimethyl-silanyloxy)-pentanal (48). General Procedure (III): Swern-Oxidation. To a solution of oxalyl chloride (3.49 g, 2.40 mL, 27.5 mmol) in CH_2Cl_2 (120 mL) at −78 °C was added dropwise a solution of DMSO (4.29 g, 3.90 mL, 54.9 mmol) in CH_2Cl_2 (6 mL). The mixture was stirred for ca. 5 min whereupon it became cloudy. A solution of alcohol **28** (5 g, 22.89 mmol) in CH_2Cl_2 (30 mL) was introduced via cannula. The resulting clear solution was stirred at −78 °C for 1 h. Triethylamine (8.80 g, 12.1 mL, 87 mmol) was added and the resulting cloudy solution was allowed to warm to room temperature. Water (100 mL) was added, producing two clear phases. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 250 mL). The combined organics were washed sequentially with 1% HCl (aq) (150 mL), water (150 mL), $NaHCO_3$ sat. (aq) (150 mL), and brine (150 mL), then dried over sodium sulfate. The solvent was removed by rotary evaporation, and the resulting oil was subjected to flash column chromatography on silica gel (hexanes/ethyl acetate, 9:1) to give the title compound as a colorless oil (4.08 g, 82%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.77 (t, 1H, J = 1.8 Hz), 3.62 (t, 2H, J = 6.1 Hz), 2.45 (dt, 2H, J = 1.7 Hz, J = 7.2 Hz), 1.76–1.64 (m, 2H), 1.60–1.49 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 202.5, 62.5, 43.5, 32.0, 25.9, 18.6, −5.3.

4-(*tert*-Butyl-dimethyl-silanyloxy)-hexanal (49). Following general procedure (III), the reaction of oxalyl chloride (1.05 g, 0.71 mL, 8.24 mmol), DMSO (1.29 g, 1.2 mL, 16,48 mmol), alcohol, **29** (1.5 g, 6.87 mmol), and triethylamine (2.64 g, 3.64 mL, 26.1 mmol) gave after flash column chromatography on silica gel (hexanes/ethyl acetate, 8:2) the title compound as a colorless oil (1.19 g, 80%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.76 (t, 1H, J = 1.8 Hz), 3.60 (t, 2H, J = 6.3 Hz), 2.43 (dt, 2H, J = 1.8 Hz, J = 7.3 Hz), 1.71–1.34 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 202.6, 62.8, 43.8, 32.4, 25.9, 25.4, 21.8, 18.6, −5.3.

2-[4-(*tert*-Butyl-dimethyl-silanyloxy)-butyl]-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (50). General Procedure (IV): N,O-Acetalization. Aldehyde **48** (4.07 g, 18.83 mmol) was dissolved in toluene (40 mL), then Na_2SO_4 (10.7 g, 75.33 mmol) and 3-aminopropanol (1.48 g, 1.52 mL, 19.77 mmol) were added, and the mixture was stirred for 15 min. A solution of Boc_2O (4.52 g, 20.72 mmol) in toluene (10 mL) was added to the reaction mixture, and it was stirred overnight. The reaction mixture was filtered through a sintered funnel and concentrated to a colorless oil. The oil was subjected to flash column chromatography on silica gel (hexanes/ethyl acetate, 9:1) to give the title compound as a colorless oil (5.90 g, 84%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.47 (t, 1H, J = 7.1 Hz), 4.02 (dd, 1H, J = 4.9 Hz, J = 13.5 Hz), 3.88 (dt, 1H, J = 3.4 Hz, J = 11.5 Hz), 3.71–3.65 (m, 1H), 3.61 (t, 2H, J = 6.4 Hz), 3.10 (dt, 1H, J = 3.6 Hz, J = 13.1 Hz), 1.97–1.71 (m, 3H), 1.60–1.25 (m, 5H), 1.46 (s, 9H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (62.5 MHz,

$CDCl_3$): δ 153.8, 82.0, 79.8, 62.9, 59.5, 36.6, 32.3, 28.7, 28.3, 25.9, 25.3, 21.2, 18.2, −5.3.

2-[5-(*tert*-Butyl-dimethyl-silanyloxy)-pentyl]-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (51). Following general procedure (IV) the reaction of 3-aminopropanol (510 mg, 6.78 mmol), Na_2SO_4 (3.67 g, 25.85 mmol), Boc_2O (1.55 g, 7.11 mmol), and **49** (1.49 g, 6.47 mmol) gave after flash column chromatography on silica gel (hexanes/ethyl acetate, 9:1) the title compound (1.47 g, 59%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.46 (t, 1H, J = 7.1 Hz), 4.02 (dd, 1H, J = 5.1 Hz, J = 13.6 Hz), 3.87 (dt, 1H, J = 3.4 Hz, J = 11.5 Hz), 3.71–3.63 (m, 1H), 3.60 (t, 2H, J = 6.4 Hz), 3.10 (dt, 1H, J = 3.6 Hz, J = 13.2 Hz), 1.96–1.68 (m, 3H), 1.56–1.14 (m, 7H), 1.45 (s, 9H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 153.7, 82.0, 79.8, 62.9, 59.4, 36.6, 32.7, 28.9, 28.3, 25.8, 25.4, 25.3, 24.6, 18.2, −5.3.

2-(3-Carboxy-propyl)-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (52). A solution of the silyl-ether **50** (584 mg, 1.56 mmol) in THF (12 mL) was added to TBAF (2.0 mL, 1.0 M sol. in THF). The reaction mixture was left stirring for 4 h at rt, and then poured into a separation funnel containing water (30 mL) and ether (50 mL). The organic phase was then separated, and the aqueous phase was extracted with ether (2 × 75 mL). The combined organic phases were dried over sodium sulfate. The solvent was removed by rotary evaporation, and the resulting oil was subjected to flash column chromatography on silica gel (hexanes/ethyl acetate, 1:1) to give the alcohol intermediate as a colorless oil (390 mg, 96%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.44 (t, 1H, J = 7.1 Hz), 3.97 (dd, 1H, J = 5.1 Hz, J = 13.6 Hz), 3.85 (dt, 1H, J = 3.5 Hz, J = 11.4 Hz), 3.69–3.65 (m, 1H), 3.61 (t, 2H, J = 6.5 Hz), 3.08 (dt, 1H, J = 3.7 Hz, J = 13.1 Hz), 1.94–1.32 (m, 8H), 1.43 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 153.8, 81.9, 79.9, 62.4, 59.5, 36.7, 32.0, 28.6, 28.2, 25.2, 21.0.

Following general procedure (II) the reaction of TEMPO (7 mg, 0.05 mmol), NaBr (18 mg, 0.18 mmol), TBABr (19 mg, 0.06 mmol), NaOCl (2.7 mL), $NaHCO_3$ (7.8 mL), and the alcohol intermediate (307 mg, 1.18 mmol) gave after flash column chromatography on silica gel (petroleum ether/ethyl acetate/AcOH, 70:30:1) the title compound as a colorless oil (287 mg, 89%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.47 (t, 1H, J = 6.9 Hz), 4.01 (dd, 1H, J = 4.9 Hz, J = 13.6 Hz), 3.87 (dt, 1H, J = 3.5 Hz, J = 11.4 Hz), 3.73–3.66 (m, 1H), 3.09 (dt, 1H, J = 3.6 Hz, J = 13.1 Hz), 2.42 (t, 2H, J = 7.2 Hz), 2.02–1.25 (m, 6H), 1.45 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 178.8, 153.8, 81.7, 80.2, 59.6, 36.7, 33.2, 28.3, 28.2, 25.2, 20.1. HRMS (ESI) calcd for $C_{13}H_{23}NO_5$ $[M + H]^+$ 274.1649, found 274.1646.

2-(4-Carboxy-butyl)-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (53). A solution of the silyl-ether **51** (1,36 g, 3.51 mmol) in THF (30 mL) was added to TBAF (5.3 mL, 1.0 M sol. in THF). The reaction mixture was left stirring for 4 h at rt, and then poured into a separation funnel containing water (75 mL) and ether (125 mL). The organic phase was then separated, and the aqueous phase was extracted with ether (2 × 200 mL). The combined organic phases were dried over sodium sulfate. The solvent was removed by rotary evaporation, and the resulting oil was subjected to flash column chromatography on silica gel (hexanes/ethyl acetate, 1:1) to give the alcohol intermediate as a colorless oil (906 mg, 94%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.47 (t, 1H, J = 7.1 Hz), 4.00 (dd, 1H, J = 5.2 Hz, J = 13.6 Hz), 3.87 (dt, 1H, J = 3.5 Hz, J = 11.4 Hz), 3.72–3.66 (m, 1H), 3.63 (t, 2H, J = 6.4 Hz), 3.09 (dt, 1H, J = 3.6 Hz, J = 13.3 Hz), 1.96–1.70 (m, 3H), 1.61–1.20 (m, 7H), 1.45 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 153.7, 81.8, 79.8, 62.2, 59.3, 36.5, 32.4, 28.7, 28.2, 25.1, 24.4, 21.0.

Following general procedure (II) the reaction of TEMPO (19 mg, 0.124 mmol), NaBr (48 mg, 0.46 mmol), TBABr (50 mg, 0.15 mmol), NaOCl (7.1 mL), $NaHCO_3$ (20.4 mL), and the alcohol intermediate (845 mg, 3.09 mmol) gave after flash column chromatography on silica gel (petroleum ether/ethyl acetate/AcOH, 70:30:1) the title compound as a colorless oil (801 mg, 90%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.46 (t, 1H, J = 7.0 Hz), 4.01 (dd, 1H, J = 5.1 Hz, J = 13.4 Hz), 3.86 (dt, 1H, J = 3.5 Hz, J = 11.4 Hz), 3.73–3.65 (m, 1H), 3.09 (dt, 1H, J = 3.7 Hz, J = 13.1 Hz), 2.36 (t, 2H, J = 7.4 Hz), 1.98–1.30 (m, 8H), 1.45 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 179.0, 153.8, 81.8, 80.1, 59.6, 36.7, 33.8, 28.6, 28.3, 25.2, 24.3, 24.2. HRMS (ESI) calcd for $C_{14}H_{25}NO_5$ $[M + H]^+$ 288.1805, found 288.1803.

(*R*)-2-((*S*)-3-Benzyloxycarbonyl-3-dibenzylamino-propyl)-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester and (*S*)-2-((*S*)-3-Benzyloxycarbonyl-3-dibenzylamino-propyl)-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (83). Following general procedure (IV) the reaction of 3-aminopropanol (744 mg, 9.9 mmol), Na_2SO_4 (4.688 g, 33 mmol), Boc_2O (2.25 g, 10.31 mmol), and aldehyde **82** (3.31 g, 8.25 mmol) gave after flash column chromatography on silica gel (heptane/ethyl acetate, 1:1) the title compound (4.15 g, 90%) as a colorless oil (∼1:1 diastereomeric mixture). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.41–7.28 (m, 15H), 5.42–5.32 (m, 1H), 5.25 (d, 1H, J = 12.3 Hz), 5.16 (d, 1H, J = 12.0 Hz), 3.95–3.90 (m, 3H), 3.73–3.47 (m, 4H), 3.45–3.35 (m, 1H), 2.98–2.87 (m, 1H), 2.1–1.35 (m, 6H), 1.42 (s, 4.5H), 1.38 (s, 4.5H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 172.4, 153.7 (0.5C), 153.7 (0.5C), 139.4 (0.5C), 139.3 (0.5C), 135.9, 128.7, 128.5, 128.5, 128.3, 128.2, 127.0, 82.1 (0.5C), 81.9 (0.5C), 80.0, 66.0, 60.9 (0.5C), 60.5 (0.5C), 59.6 (0.5C), 59.4 (0.5C), 54.5 (0.5C), 54.4 (0.5C), 36.6 (0.5C), 36.6 (0.5C), 28.3 (4.5C), 28.2 (4.5C), 26.1 (0.5C), 25.7 (0.5C), 25.2 (0.5C), 25.1 (0.5C), 25.0 (0.5C), 24.8 (0.5C). HRMS (ESI) calcd for $C_{34}H_{43}N_2O_5$ $[M + H]^+$ 559.3172, found 559.3198.

(*R*)-2-((*S*)-3-Carboxy-3-dibenzylamino-propyl)-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester and (*S*)-2-((*S*)-3-Carboxy-3-dibenzylamino-propyl)-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (84). Acetal **83** (1.12 g, 2 mmol) was dissolved in ethanol (20 mL), and potassium hydroxyde (146 mg, 2.6 mmol) was added. The mixture was left under stirring overnight and then acidified slowly to pH 4 with 1.0 M HCl (aq). The mixture was then extracted with CH_2Cl_2 (3 × 75 mL). The combined extracts were dried over Na_2SO_4 and concentrated to an oil which gave after flash column chromatography on silica gel (ethyl acetate/heptane/AcOH, 16:4:1) the title compound (524 mg, 56%) as a colorless oil (∼1:1 diastereomeric mixture). ^{1}H NMR (250

MHz, $CDCl_3$): δ 7.42–7.26 (m, 10H), 5.40–5.27 (m, 1H), 3.97–3.48 (m, 8H), 3.12–2.99 (m, 1H), 2.08–1.60 (m, 4H), 1.53–1.36 (m, 2H), 1.45 (s, 4.5H), 1.41 (s, 4.5H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 175.4 (0.5C), 175.3 (0.5C), 155.6 (0.5C), 155.5 (0.5C), 140.0 (0.5C), 139.9 (0.5C), 130.2, 129.5, 128.5, 83.6 (0.5C), 83.2 (0.5C), 81.6, 62.5 (0.5C), 62.5 (0.5C), 60.8 (0.5C), 60.6 (0.5C), 55.7 (0.5C), 55.6 (0.5C), 38.1 (0.5C), 37.9 (0.5C), 28.7, 27.4 (0.5C), 27.0 (0.5C), 26.3, 25.9 (0.5C), 25.6 (0.5C). HRMS (ESI) calcd for $C_{27}H_{37}N_2O_5$ $[M + H]^+$ 469.2702, found 469.2677.

Characterization of Cyclization Products

[(*S*)-2-({(4*S*,7*S*,8a*S*)-7-[(*S*)-2-Amino-3-(4-hydroxy-phenyl)-propionylamino]-6-oxo-hexahydro-pyrrolo[2,1-*b*][1,3]oxazine-4-carbonyl}-amino)-3-phenyl-propionylamino]-acetic acid (15). $>^1$H NMR (250 MHz, DMSO-d_6): δ 9.05 (d, 1H, $J = 7.5$ Hz), 8.47 (t, 1H, $J = 5.8$ Hz), 8.11 (s, 3H), 7.91 (d, 1H, $J = 8.7$ Hz), 7.30–7.19 (m, 5H), 7.11 (d, 2H, $J = 8.5$ Hz), 6.73 (d, 2H, $J = 8.5$ Hz), 4.88–4.77 (m, 1H), 4.54 (d, 1H, $J = 6.1$ Hz), 4.45 (d, 1H, $J = 5.2$ Hz), 4.34–4.25 (m, 1H), 4.03–3.98 (m, 1H), 3.81 (dd, 2H, $J =$ 1.4 Hz, $J = 5.8$ Hz), 3.71 (dd, 1H, $J = 3.6$ Hz, $J = 11.5$ Hz), 3.19–2.86 (m, 5H), 2.11–1.87 (m, 3H), 1.71–1.56 (m, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 171.3, 170.9, 170.8, 168.5, 168.3, 156.6, 137.8, 130.5, 129.1, 128.0, 126.3, 124.3, 115.3, 83.2, 63.3, 53.4, 50.1, 48.8, 40.60, 37.3, 36.1, 31.6, 25.4. HRMS (ESI) calcd for $C_{28}H_{34}N_5O_8$ $[M + H]^+$ 568.2407, found 568.2391.

((6*S*,12b*S*)-2,3-Dimethoxy-8-oxo-5,6,8,12b-tetrahydro-isoindolo[1,2-*a*]isoquinoline-6-carbonyl)-amino]-acetic acid (19). ^{1}H NMR (250 MHz, DMSO-d_6): δ 12.55 (bs, 1H), 8.56 (t, 1H, $J = 5.9$ Hz), 8.19 (d, 1H, $J = 7.6$ Hz), 7.79–7.71 (m, 2H), 7.58 (t, 1H, $J = 7.4$ Hz), 7.18 (s, 1H), 6.85 (s, 1H), 5.87 (s, 1H), 4.94 (dd, 1H, $J = 4.9$ Hz, $J = 6.4$ Hz), 3.78 (s, 3H), 3.75 (d, 2H, $J = 6.3$ Hz), 3.72 (s, 3H), 3.19 (dd, 1H, J = 4.7 Hz, $J = 15.9$ Hz), 3.03 (dd, 1H, $J = 6.7$ Hz, $J = 15.8$ Hz). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 170.9, 170.2, 167.4, 148.0, 147.4, 144.9, 132.0, 131.4, 128.4, 125.5, 124.9, 124.3, 123.1, 112.2, 109.0, 57.0, 55.7, 55.4, 50.9, 40.6, 30.2. HRMS (ESI) calcd for $C_{21}H_{20}N_2O_6$ $[M + H]^+$ 397.1400, found 397.1362.

[((2*R*,3*S*,9b*S*)-2-Methyl-5-oxo-2,3,5,9b-tetrahydro-oxazolo[2,3-*a*]isoindole-3-carbonyl)-amino]-acetic acid (20). ^{1}H NMR (250 MHz, DMSO-d_6): δ 12.65 (s, 1H), 8.62 (t, 1H, $J = 5.9$ Hz), 7.79–7.63 (m, 4H), 6.05 (s, 1H), 4.43 (p, 1H, $J = 6.1$ Hz), 3.97 (d, 1H, $J = 7.1$ Hz), 3.80 (d, 2H, $J =$ 5.9 Hz), 1.38 (d, 3H, $J = 6.1$ Hz). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 172.4, 170.6, 169.4, 141.9, 133.3, 132.1, 130.9, 124.7, 123.9, 90.8, 83.4, 62.9, 40.6, 19.5. HRMS (ESI) calcd for $C_{14}H_{14}N_2O_5$ $[M + H]^+$ 291.0982, found 291.0972.

[((4*S*,10b*S*)-6-Oxo-3,4,6,10b-tetrahydro-2*H*-[1,3]oxazino[2,3-*a*]isoindole-4-carbonyl)-amino]-acetic acid (21). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.52 (t, 1H, $J = 5.9$ Hz), 7.79–7.58 (m, 4H), 5.89 (s, 1H), 4.90 (d, 1H, $J = 6.0$ Hz), 4.03 (dd, 1H, $J = 3.6$ Hz, $J = 11.7$ Hz), 3.84 (m, 2H), 3.70 (dd, 1H, $J = 5.7$ Hz, $J = 17.3$ Hz), 2.16 (dd, 1H, $J = 1.1$ Hz, $J = 13.7$ Hz), 1.83 (m, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 170.9, 170.006, 165.8, 141.8, 132.2, 131.7, 129.8, 123.7, 122.9, 83.1, 63.8, 49.2, 40.8, 26.1. HRMS (ESI) calcd for $C_{14}H_{14}N_2O_5$ $[M + H]^+$ 291.0982, found 291.0979.

[((5*S*,10b*R*)-3-Oxo-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinoline-5-carbonyl)-amino]-acetic acid (23a). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.30 (t, 1H, $J = 5.8$ Hz), 7.26–7.13 (m, 4H), 4.95 (t, 1H, $J = 7.8$ Hz), 4.76 (dd, 1H, $J = 3.2$ Hz, $J = 7.0$ Hz), 3.68 (d, 1H, $J = 5.9$ Hz), 3.18 (dd, 1H, $J = 3.2$ Hz, $J = 16.2$ Hz), 2.96 (dd, 1H, $J = 7.1$ Hz, J = 16.2 Hz), 2.75–2.54 (m, 2H), 2.31–2.21 (m, 1H), 1.84–1.69 (m, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.2, 170.9, 169.8, 137.2, 131.6, 128.6, 126.5, 124.5, 54.1, 49.2, 40.8, 30.9, 29.9, 27.0. MS (ES) calcd for $C_{15}H_{15}N_2O_4$ $[M - H]^-$ 287.1, found 287.0.

[((6*S*,11b*R*)-4-Oxo-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-6-carbonyl)-amino]-acetic acid (23b). ^{1}H NMR (250 MHz, DMSO-d_6): δ 12.42 (bs, 1H), 8.22 (t, 1H, $J = 5.8$ Hz), 7.19 (d, 4H, $J = 33.6$ Hz), 5.30 (dd, 1H, $J = 4.4$ Hz, $J = 6.0$ Hz), 4.80 (dd, 1H, $J = 4.2$ Hz, $J = 10.1$ Hz), 3.66 (d, 2H, $J = 5.9$ Hz), 3.16 (dd, 1H, $J =$ 4.3 Hz, $J = 15.9$ Hz), 2.93 (dd, 1H, $J = 6.1$ Hz, $J = 15.8$ Hz), 2.44–2.21 (m, 3H), 1.96–1.8 (m, 3H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 171, 170.2, 169.4, 136.9, 132.7, 128.3, 126.3, 126.3, 124.7, 53.9, 50.6, 40.6, 31.9, 29.9; 29.8, 18.7. HRMS (ESI) calcd for $C_{16}H_{19}N_2O_4$ $[M + H]^+$ 303.1345, found 303.1332.

[((5*S*,10b*R*)-8,9-Dimethoxy-3-oxo-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinoline-5-carbonyl)-amino]-acetic acid (23d). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.29 (t, 1H, $J = 5.9$ Hz), 6.72 (s, 1H), 6.71 (s, 1H), 4.86 (t, 1H, $J =$ 7.7 Hz), 4.77 (dd, 1H, $J = 2.3$ Hz, $J = 7.0$ Hz), 3.72 (s, 3H), 3.71 (s, 3H), 3.67 (d, 2H, $J = 5.9$ Hz), 3.14 (dd, 1H, J = 2.1 Hz, $J = 16.1$ Hz), 2.85 (dd, 1H, $J = 7.1$ Hz, $J = 16.0$ Hz), 2.74–2.54 (m, 2H), 2.25 (dd, 1H, $J = 8.5$ Hz, $J = 15.3$ Hz), 1.76–1.61 (m, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.3, 170.9, 169.7, 147.7, 147.4, 128.8, 123.2, 111.9, 108.2, 55.5, 55.4, 53.9, 49.1, 40.8, 31.0, 29.2, 27.5. MS (ES) calcd for $C_{17}H_{19}N_2O_6$ $[M - H]^-$ 347.0, found 347.6.

[((6*S*,11b*R*)-9,10-Dimethoxy-4-oxo-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-6-carbonyl)-amino]-acetic acid (23e). ^{1}H NMR (250 MHz, DMSO-d_6): δ 12.49 (bs, 1H), 8.20 (t, 1H, $J = 5.9$ Hz), 6.77 (s, 1H), 6.69 (s, 1H), 5.38 (dd, 1H, $J = 3.2$ Hz, $J = 5.9$ Hz), 4.73 (dd, 1H, $J =$ 3.6 Hz, $J = 10.4$ Hz), 3.71 (s, 6H), 3.65 (d, 2H, $J = 5.9$ Hz), 3.11 (dd, 1H, $J = 3.2$ Hz, $J = 15.8$ Hz), 2.80 (dd, 1H, $J = 5.9$ Hz, $J = 15.7$ Hz), 2.44 (m, 2H), 2.35–2.21 (m, 1H), 1.96–1.76 (m, 2H), 1.60–1.44 (m, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 171, 170.1, 169.4, 147.3, 147.3, 128.4, 124.4, 111.6, 108.9, 55.5, 55.4, 53.8, 50.2, 40.7, 31.9, 30.7, 29.2, 18.8. HRMS (ESI) calcd for $C_{18}H_{22}N_2O_6$ $[M + H]^+$ 363.1556, found 363.1507.

[((5*S*,11b*R*)-3-Oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole-5-carbonyl)-amino]-acetic acid (45). ^{1}H NMR (250 MHz, DMSO-d_6): 11.14 (s, 1H), 8.29 (t, 1H, J = 5.8 Hz), 7.38 (d, 1H, $J = 7.5$ Hz), 7.30 (d, 1H, $J = 7.8$ Hz), 7.05 (dt, 1H, $J = 1.3$ Hz, $J = 7.4$ Hz), 6.96 (dt, 1H, J = 1.0 Hz, $J = 7.6$ Hz), 5.13 (t, 1H, $J = 7.4$ Hz), 5.02 (d, 1H, $J = 6.9$ Hz), 3.66 (dd, 2H, $J = 2.8$ Hz, $J = 5.8$ Hz), 3.40 (d, 1H, $J = 15.5$ Hz), 2.80 (ddd, 1H, $J = 1.5$ Hz, $J =$ 7.2 Hz, $J = 15.5$ Hz), 2.70–2.56 (m, 2H), 2.36–2.24 (m,

1H), 1.83–1.71 (m, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.5, 170.9, 169.7, 136.0, 133.6, 126.3, 120.8, 118.4, 117.7, 111.0, 103.8, 51.6, 49.2, 40.9, 30.9, 26.1, 22.2. MS (ESI) calcd for $C_{17}H_{16}N_3O_4$ [M – H]$^-$ 326.1, found 326.1.

{(*S*)-2-[((5*S*,11b*R*)-4-Oxo-1,3,4,5,6,11b-hexahydro-2*H*-11-thia-4a-aza-benzo[*a*]fluorene-5-carbonyl)-amino]-3-phenyl-propionylamino}-acetic acid (64). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.26–8.18 (m, 2H), 7.87 (dd, 1H, J = 1.7 Hz, J = 6.9 Hz), 7.63 (dd, 1H, J = 1.4 Hz, J = 6.7 Hz), 7.43–7.19 (m, 7H), 5.75 (d, 1H, J = 5.5 Hz), 4.62–4.52 (m, 1H), 3.72 (dd, 2H, J = 1.1 Hz, J = 5.6 Hz), 3.67–3.59 (m, 1H), 3.40 (d, 1H, J = 15.7 Hz), 3.10 (dd, 1H, J = 3.8 Hz, J = 13.9 Hz), 2.91 (dd, 1H, J = 12.2 Hz, J = 13.6 Hz), 2.62–2.53 (m, 1H), 2.29–1.36 (m, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 171.8, 171.4, 169.5, 169.2, 138.7, 138.6, 138.2, 137.1, 129.4, 128.5, 127.7, 126.5, 124.7, 124.6, 122.8, 121.3, 54.5, 51.8, 49.8, 41.6, 36.7, 33.0, 31.7, 23.6, 18.6. HRMS (ESI) calcd for $C_{27}H_{27}N_3O_5SNa$ [M + Na]$^+$ 528.1569, found 528.1574.

{(*S*)-2-[((5*S*,10a*R*)-7-Oxo-4,7,8,9,10,10a-hexahydro-5*H*-thieno[3,2-*a*]quinolizine-5-carbonyl)-amino]-3-phenyl-propionylamino}-acetic acid (65). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.27 (t, 1H, J = 5.6 Hz), 8.13 (d, 1H, J = 8.3 Hz), 7.27–7.18 (m, 6H), 6.53 (d, 1H, J = 5.2 Hz), 5.67 (d, 1H, J = 4.9 Hz, 1H), 4.55–4.47 (m, 1H), 3.73 (dd, 2H, J = 2.6 Hz, J = 5.6 Hz), 3.56 (dd, 1H, J = 4.1 Hz, J = 10.3 Hz), 3.29 (d, 1H, J = 16.0 Hz), 3.07 (dd, 1H, J = 3.8 Hz, J = 13.8 Hz), 2.91 (dd, 1H, J = 11.6 Hz, J = 13.7 Hz), 2.61 (dd, 1H, J = 5.9 Hz, J = 15.7 Hz), 2.25–1.17 (m, 6H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 171.4, 170.9, 169.2, 168.6, 138.0, 135.3, 131.7, 129.0, 127.8, 126.0, 123.9, 123.1, 54.1, 52.2, 49.7, 41.0, 36.2, 32.4, 29.8, 24.2, 18.1. HRMS (ESI) calcd for $C_{23}H_{26}N_3O_5S$ [M + H]$^+$ 456.1588, found 456.1584.

{(*S*)-2-[((5*S*,9a*R*)-6-Oxo-4,6,7,8,9,9a-hexahydro-5*H*-3-oxa-5a-aza-cyclopenta[*a*]naphthalene-5-carbonyl)-amino]-3-phenyl-propionylamino}-acetic acid (66). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.30 (t, 1H, J = 5.6 Hz), 8.08 (d, 1H, J = 8.3 Hz), 7.38 (d, 1H, J = 1.5 Hz), 7.21 (m, 5H), 6.06 (d, 1H, J = 1.8 Hz), 5.70 (d, 1H, J = 5.8 Hz), 4.52 (m, 2H), 3.78 (dd, 2H, J = 1.9 Hz, J = 5.6 Hz), 3.34 (dd, 1H, J = 3.6 Hz, J = 10.5 Hz), 2.98 (m, 3H), 1.91 (m, 6H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 171.5, 170.1, 169.3, 168.7, 146.63, 141.5, 137.9, 129, 127.91, 126.1, 118.1, 107.2, 54, 49.9, 49.7, 40.7, 36.3, 32.6, 29.5, 23.1, 18.1. HRMS (ESI) calcd for $C_{23}H_{26}N_3O_6$ [M + H]$^+$ 440.1816, found 440.1819.

{(*S*)-2-[((5*S*,10a*R*)-7-Oxo-4,7,8,9,10,10a-hexahydro-5*H*-thieno[2,3-*a*]quinolizine-5-carbonyl)-amino]-3-phenyl-propionylamino}-acetic acid (67). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.25 (t, 1H, J = 5.6 Hz), 8.14 (d, 1H, J = 8.3 Hz), 7.26–7.20 (m, 6H), 6.72 (d, 1H, J = 5.1 Hz), 5.59 (d, 1H, J = 5.6 Hz), 4.61–4.51 (m, 1H), 3.74 (dd, 2H, J = 2.2 Hz, J = 5.5 Hz), 3.65 (dd, 1H, J = 5.0 Hz, J = 9.0 Hz), 3.18 (d, 1H, J = 16.0 Hz), 3.09 (dd, 1H, J = 3.8 Hz, J = 13.9 Hz), 2.91 (dd, 1H, J = 11.9 Hz, J = 13.6 Hz), 2.54–1.34 (m, 7H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 171.4, 171.0, 169.0, 168.9, 138.0, 135.5, 132.5, 128.9, 127.9, 126.9, 126.0, 123.3, 54.0, 51.3, 49.6, 41.0, 36.3, 32.4, 31.6, 24.8, 18.0. HRMS (ESI) calcd for $C_{23}H_{26}N_3O_5S$ [M + H]$^+$ 456.1588, found 456.1577.

{(*S*)-2-[((3*S*,8a*S*)-5-Oxo-hexahydro-oxazolo[3,2-*a*]pyridine-3-carbonyl)-amino]-3-phenyl-propionylamino}-acetic acid (75). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.31 (t, 1H, J = 5.7 Hz), 8.16 (d, 1H, J = 8.6 Hz), 7.32–7.17 (m, 5H), 4.63–4.54 (m, 2H), 4.48 (t, 1H, J = 7.9 Hz), 4.15 (t, 1H, J = 8.5 Hz), 3.77 (d, 2H, J = 5.9 Hz), 3.38 (dd, 1H, J = 7.6 Hz, J = 8.6 Hz), 3.07 (dd, 1H, J = 4.5 Hz, J = 13.8 Hz), 2.83 (dd, 1H, J = 9.8 Hz, J = 13.8 Hz), 2.36–2.10 (m, 3H), 1.85–1.61 (m, 2H), 1.41–1.24 (m, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 170.9, 170.8, 168.8, 168.2, 137.5, 129.2, 127.8, 126.1, 87.6, 67.1, 56.1, 53.4, 40.7, 37.2, 30.7, 27.4, 16.5. HRMS (ESI) calcd for $C_{19}H_{24}N_3O_6$ [M + H]$^+$ 390.1660, found 390.1670.

{(*S*)-2-[((2*R*,3*S*,8a*S*)-2-Methyl-5-oxo-hexahydro-oxazolo[3,2-*a*]pyridine-3-carbonyl)-amino]-3-phenyl-propionylamino}-acetic acid (76). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.26–8.23 (m, 2H), 7.25–7.17 (m, 5H), 4.74 (dd, 1H, J = 4.3 Hz, J = 9.1 Hz), 4.63–4.54 (m, 1H), 3.84 (d, 1H, J = 7.8 Hz), 3.76 (d, 2H, J = 6.0 Hz), 3.58–3.48 (m, 1H), 3.10 (dd, 1H, J = 4.5 Hz, J = 13.7 Hz), 2.86 (dd, 1H, J = 10.2 Hz, J = 13.7 Hz), 2.36–2.10 (m, 3H), 184–1.67 (m, 2H), 1.40–1.25 (m, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 170.8, 168.5, 168.4, 137.7, 129.2, 127.8, 126.1, 87.6, 75.9, 63.3, 53.4, 40.8, 37.0, 30.6, 27.6, 18.6, 16.6. HRMS (ESI) calcd for $C_{20}H_{26}N_3O_6$ [M + H]$^+$ 404.1816, found 404.1811.

{(*S*)-2-[((4*S*,9a*S*)-6-Oxo-hexahydro-pyrido[2,1-*b*][1,3]oxazine-4-carbonyl)-amino]-3-phenyl-propionylamino}-acetic acid (77). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.39 (t, J = 5.7 Hz, 1H), 7.99 (d, 1H, J = 8.6 Hz), 7.30–7.16 (m, 5H), 5.14 (d, 1H, J = 5.1 Hz), 4.80–4.70 (m, 1H), 3.92 (t, 1H, J = 4.3 Hz), 3.78 (dd, 2H, J = 2.1 Hz, J = 5.7 Hz), 372–3.65 (m, 1H), 322–3.09 (m, 2H), 2.90 (dd, 1H, J = 11.3 Hz, J = 13.8 Hz), 2.31–2.18 (m, 2H), 2.00–1.95 (m, 1H), 1.84–1.41 (m, 5H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 171.4, 170.9, 169.5, 169.4, 138, 129, 127.9, 126.1, 83, 64.1, 53.5, 49.9, 40.8, 36.7, 32.5, 28.3, 25.5, 16.5. HRMS (ESI) calcd for $C_{20}H_{26}N_3O_6$ [M + H]$^+$ 404.1816, found 404.1812.

(3*S*,8a*S*)-3-[(*S*)-1-(Carboxymethyl-carbamoyl)-2-phenyl-ethylcarbamoyl]-5-oxo-hexahydro-imidazo[1,2-*a*]pyridine-1-carboxylic acid *tert*-butyl ester (78). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.41 (t, 1H, J = 5.6 Hz), 8.02 (d, 1H, J = 8.7 Hz), 7.23–7.12 (m, 5H), 4.82 (d, 1H, J = 6.8 Hz), 4.62–4.48 (m, 2H), 3.76 (dd, 2H, J = 3.0 Hz, J = 5.6 Hz), 3.64 (d, 1H, J = 10.4 Hz), 3.32–3.21 (m, 1H), 3.05 (dd, 1H, J = 4.1 Hz, J = 13.8 Hz), 2.80 (dd, 1H, J = 10.0 Hz, J = 13.7 Hz), 2.43–2.12 (m, 3H), 1.85–1.59 (m, 2H), 1.39 (s, 9H), 1.31–1.13 (m, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 171.4, 169.5, 168.3, 152.8, 138, 129.5, 128.3, 126.6, 80, 70.9, 55.5, 54, 46.3, 41.3, 4.9, 30.8, 28.4, 17.8. HRMS (ESI) calcd for $C_{19}H_{25}N_4O_5$ [M – $C_5H_7O_2$]$^+$ 389.1825, found 389.1283.

(4*S*,9a*R*)-4-[(*S*)-1-(Carboxymethyl-carbamoyl)-2-phenyl-ethylcarbamoyl]-6-oxo-octahydro-pyrido[1,2-*a*]pyrazine-2-carboxylic acid *tert*-butyl ester (79). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.27 (t, 1H, J = 5.7 Hz), 7.86 (d, 1H, J = 8.2 Hz), 7.21–7.15 (m, 5H), 5.23 (dd, 1H, J = 3.9 Hz, J = 10.4

Hz), 4.96 (dd, 1H, $J = 5.2$ Hz, $J = 7.0$ Hz), 4.52 (dt, 1H, $J = 5.1$ Hz, $J = 8.9$ Hz), 3.73 (d, 2H, $J = 5.7$ Hz), 3.65 (dd, 1H, $J = 5.8$ Hz, $J = 13.9$ Hz), 3.05 (dd, 1H, $J = 5.0$ Hz, $J = 13.8$ Hz), 2.85 (dd, 1H, $J = 9.2$ Hz, $J = 13.8$ Hz), 2.77–2.65 (m, 1H), 2.33–2.15 (m, 3H), 1.87–1.40 (m, 5H), 1.33 (s, 9H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 171.1, 170.9, 170.0, 169.6, 152.9, 137.7, 128.9, 127.9, 126.1, 79.1, 66.2, 54.0, 48.1, 40.7, 37.1, 35.9, 31.8, 28.1, 27.9, 27.2, 24.0, 16.6. HRMS (ESI) calcd for $C_{25}H_{35}N_4O_7$ $[M + H]^+$ 503.2500, found 503.2515.

{(*S*)-2-[((3*R*,8a*S*)-5-Oxo-hexahydro-thiazolo[3,2-*a*]pyridine-3-carbonyl)-amino]-3-phenyl-propionylamino}-acetic acid (81). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.28 (t, 1H, $J = 5.8$ Hz), 8.16 (d, 1H, $J = 8.4$ Hz), 7.26–7.16 (m, 5H), 4.99 (dd, 1H, $J = 5.8$ Hz, $J = 7.9$ Hz), 4.60–4.45 (m, 2H), 3.76 (d, 2H, $J = 5.7$ Hz), 3.17–3.04 (m, 2H), 2.93–2.82 (m, 2H), 2.32–2.14 (m, 3H), 1.86–1.48 (m, 3H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 170.9, 170.8, 169.1, 168, 137.7, 129.1, 127.8, 126.1, 62.2, 60.9, 53.7, 40.7, 36.9, 30.9, 30.6, 28.3, 19.5. HRMS (ESI) calcd for $C_{19}H_{24}N_3O_5S$ $[M + H]^+$ 406.1431, found 406.1438.

((3*S*,6*S*,11b*R*)-3-Dibenzylamino-9,10-dimethoxy-4-oxo-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-6-carbonyl)-amino]-acetic acid (87). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.26 (s, 1H), 7.49–7.34 (m, 10H), 6.79 (s, 2H), 5.03 (t, 1H, $J = 5.2$ Hz), 4.77 (dd, 1H, $J = 3.6$ Hz, $J = 11.1$ Hz), 4.31–4.10 (m, 5H), 3.76 (dd, 2H, $J = 6.0$, $J = 2.3$ Hz), 3.73 (s, 6H), 3.01 (d, 2H, $J = 6.2$ Hz), 2.78–2.67 (m, 1H), 2.34–2.23 (m, 2H), 1.80–1.59 (m, 1H). HRMs (ESI) calcd for $C_{32}H_{36}N_3O_6$ $[M + H]^+$ 558.2604, found 558.2603.

[((4*S*,7*S*,9a*S*)-7-Dibenzylamino-6-oxo-hexahydro-pyrido[2,1-*b*][1,3]oxazine-4-carbonyl)-amino]-acetic acid (88). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.28 (t, 1H, $J = 5.2$ Hz), 7.43–7.31 (m, 10H), 5.15 (d, 1H, $J = 5.0$ Hz), 4.97 (dd, 1H, $J = 4.7$ Hz, $J = 9.2$ Hz), 4.14–4.01 (m, 4H), 3.90–3.49 (m, 5H), 2.23–1.92 (m, 5H), 1.60–1.46 (m, 1H). HRMS (ESI) calcd for $C_{25}H_{30}N_3O_5$ $[M + H]^+$ 452.2185, found 452.2175.

Acknowledgment. The Danish National Research Foundation is gratefully acknowledged for financial support.

Supporting Information Available. Analytical data (HPLC, MS, and NMR) for building blocks and compounds cleaved from the solid support. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC700097K