Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 64 (2008) 1114–1134
Tetrahedron
www.elsevier.com/locate/tet

A convergent synthesis of enantiopure bicyclic scaffolds through multicomponent Ugi reaction

Luca Banfi, Andrea Basso, Giuseppe Guanti, Silvia Merlo, Claudio Repetto, Renata Riva*

Dipartimento di Chimica e Chimica Industriale, Via Dodecaneso 31, I-16146 Genova, Italy

Received 14 September 2007; accepted 17 October 2007
Available online 22 October 2007

Dedicated to Professor Csaba Szántay on the occasion of his 80th birthday

Abstract

An efficient and convergent Ugi synthesis of enantiomerically pure *N*-acyl-2,5-disubstituted pyrrolidines was coupled with an appropriate secondary transformation to give two series of bicyclic derivatives, namely hexahydro pyrrolo-oxazocinediones and -diazepinediones.

Keywords: Multicomponent Ugi reaction; Cyclic imine; Pyrrolidine; Peptidomimetics; Acylation

1. Introduction

The synthesis of non-aromatic heterocyclic medium-sized rings, containing at least one nitrogen atom,[1,2] or of their bicyclic derivatives,[3,4] has gained a noticeable importance in the last decades, as well documented in the literature. In particular, some of these structures have been used as conformationally constrained peptidomimetics. When joined to small oligopeptide sequences, they may act as 'external reverse turn inducers'[5] influencing their three dimensional structure and hence their complexation with various biological targets.

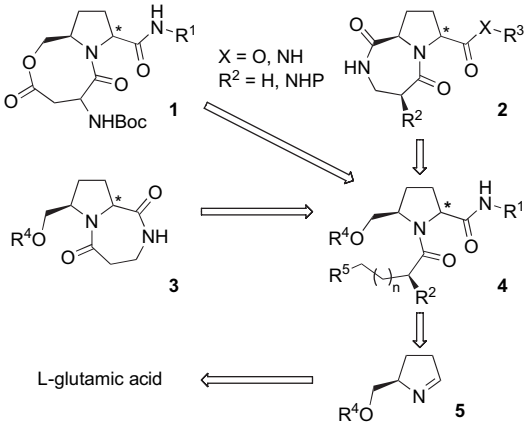
For example, such systems have been successfully used as external scaffolds for assembling macrocyclic derivatives incorporating the RGD sequence, which found application as inhibitors of integrins.[2,4,6]

An important aspect, when dealing with new molecules of potential biological activity, is represented by the possibility to produce different compounds, characterized by chemical and/or stereochemical diversity, through a similar protocol. A possibility for multidiversity generation is represented by multicomponent reactions (MCRs),[7] which are extremely convergent, leading to very complex structures in just one step. Among MCRs, those based on the peculiar reactivity of isocyanides, such as the Ugi[8] and the Passerini[9] reactions, have found many interesting applications, also in the industry.[10] A drawback of these reactions is the fact that only acyclic structures, respectively, a peptide and a depsipeptide, can be obtained at first sight. However, heterocyclic compounds can be prepared by post-condensation cyclization steps, provided that the acyclic moiety is endowed with one or two suitably positioned additional functional groups.[11] In this field our group has reported several new convergent syntheses of heterocycles just coupling a MCR with a secondary transformation.[2,12,13]

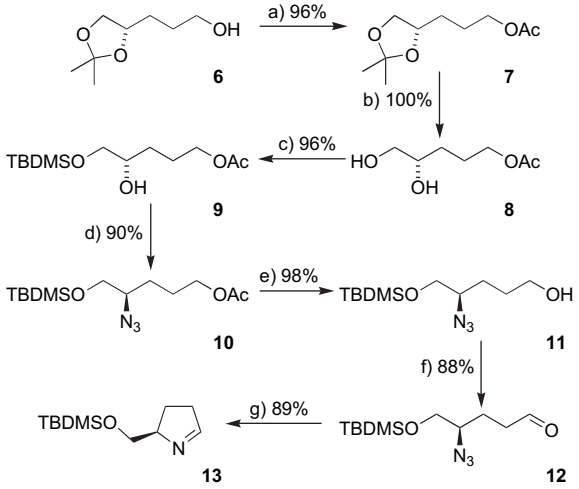
We recently reported in preliminary form the synthesis of a small library of *N*-acyl-2,5-disubstituted pyrrolidines **4** through an intramolecular variant of the Ugi reaction employing pyrrolines **5** as cyclic imines (Scheme 1),[14] using various isocyanides and carboxylic acids. The reaction was found to be of general scope, affording good to excellent yields in all cases. By employing a carboxylic acid containing an additional function R^5 a subsequent cyclization is in principle possible, involving either the protected hydroxymethyl group or the amide function. The effectiveness of this approach was already preliminary proved, by synthesizing two diastereomeric lactones **1**.[14] We now report full details on the synthesis of hexahydro pyrrolo-oxazocinediones **1** and extend

* Corresponding author. Tel.: +39 010 3536126; fax: +39 010 3536118.
E-mail address: riva@chimica.unige.it (R. Riva).

0040-4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.10.058



Scheme 1. Retrosynthetic analysis.



Scheme 2. (a) Ac_2O, Py, rt; (b) AcOH, H_2O, rt; (c) $^tBuMe_2SiCl$, imidazole, DMAP, THF, rt; (d) (i) MsCl, Et_3N, CH_2Cl_2, −30 °C; (ii) NaN_3, DMF, 65 °C; (e) KOH, MeOH, 0 °C; (f) $(COCl)_2$, DMSO, Et_3N, −78 °C to −50 °C; (g) PPh_3, THF, 50 °C.

the scope of this general strategy to the preparation of hexahydro pyrrolodiazepinediones **2** and **3**.

While, to the best of our knowledge, bicyclic derivatives **1** were unknown, there are only three examples of hexahydro pyrrolodiazepinediones having the basic skeleton of **2** and **3**;[15–17] however, they showed interesting nootropic activity[16] or were studied as inhibitors of aminopeptidase P.[17]

2. Results and discussion

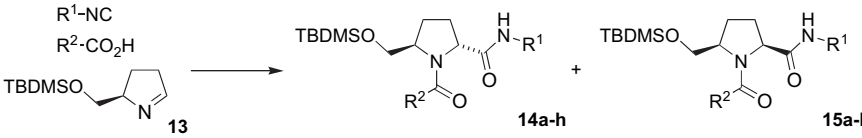
First of all we developed an enantioselective synthesis of the key intermediate **13** (Scheme 2).[14] Toward that goal we started from L-glutamic acid, which was transformed into compound **6**.[18] An appropriate choice of protecting groups of the three alcoholic functionalities permitted an independent manipulation of them, allowing the preparation of azido aldehyde **12** in excellent yield. The five-membered ring was formed as the last step through a Staudinger/aza-Wittig reaction[19] and compound **13** was isolated in 64% overall yield from **6**,[20] without racemization.[21]

Pyrroline **13** was then submitted to a series of Ugi condensations with various isocyanides and carboxylic acids.[22] In Table 1 we show only the results obtained with functionalized carboxylic acids or isocyanides, whose structures were chosen according to our present purpose, that is, the synthesis of bicyclic system endowed with further appendages.

Other simpler examples of these Ugi condensations may be found in our preliminary communication.[14] Concerning the isocyanides, we employed commercially available benzylisocyanide (entries 1–4) and *p*-methoxyphenylisocyanide (entry 8)[23] and also the 'convertible' isocyanides proposed by Ugi (entries 5–6 and 10)[24] and Linderman (entry 7),[25] which have been prepared by the reported procedures.[26] As carboxylic acids, apart from benzoic acid (entry 9), we used enantiomerically pure protected α- and β-aminoacids. They were commercially available with the exception of the orthogonally protected 2,3-diaminopropanoic acid (entry 4). This compound was prepared in enantiopure form following a known procedure involving the Hofmann rearrangement of Boc-L-asparagine.[27]

The yields ranged from moderate to excellent (Table 1), while the diastereomeric ratio was always moderate, according

Table 1
Ugi reactions employing pyrroline **13**

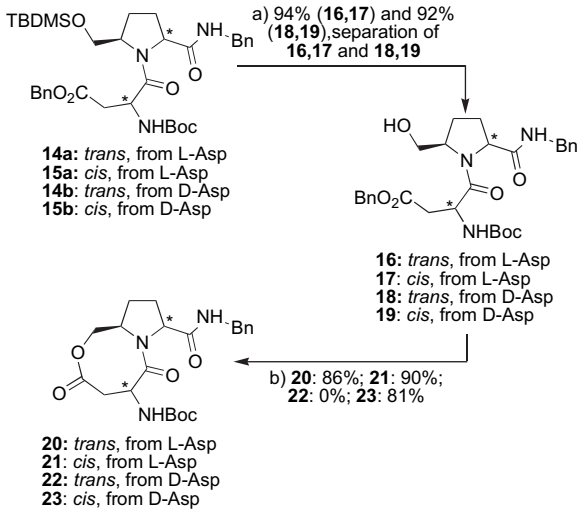


Entry[a]	R^1–NC	R^2–CO_2H	Product	Yield % (**14**/**15**)	dr (**14**/**15**)[b]
1	$PhCH_2$–NC	Boc-L-Asp(OBn)	**14**, **15a**	85	66:34
2	$PhCH_2$–NC	Boc-D-Asp(OBn)	**14**, **15b**	79	68:32
3	$PhCH_2$–NC	Z-β-Ala	**14**, **15c**	66	68:32
4	$PhCH_2$–NC	*S*-(NHZ)CH_2CH(NHBoc)–CO_2H	**14**, **15d**	52	64:36
5	$MeOCO_2CH_2CMe_2$–NC	Boc-L-Asp(OBn)	**14**, **15e**	66	63:37
6	$MeOCO_2CH_2CMe_2$–NC	Z-L-Asp(O^{t}Bu)	**14**, **15f**	67	60:40
7	(*o*-CH_2OTBDMS)C_6H_4–NC	Z-β-Ala	**14**, **15g**	47	65:35
8	(*p*-OMe)C_6H_4–NC	Z-β-Ala	**14**, **15h**	75	64:36
9	$MeOCO_2CH_2CMe_2$–NC	Ph–CO_2H	**14**, **15i**	81	68:32

[a] All reactions were carried out in MeOH (≈0.3 M).
[b] See Section 4.

to the general trend observed in the Ugi reaction.[7] The prevailing diastereoisomer was always the trans one. The relative configuration was demonstrated by strong NMR analogies with a previously prepared simpler analog, whose configuration was proved by chemical correlation.[14] Moreover, as shown later, for most of the compounds **14** and **15** the configuration has been further confirmed unambiguously. The separation of the two epimers was usually not easy and, in some cases, even impossible; however, the separation became easier and more convenient on the corresponding alcohols after TBDMS removal.

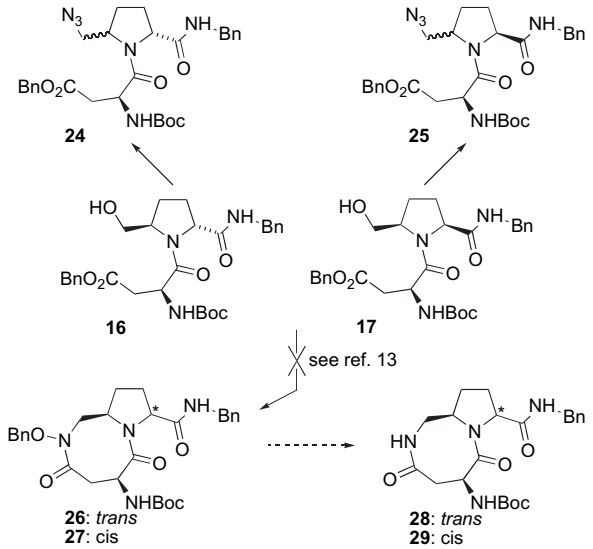
As the first synthetic application of derivatives **14** and **15**, we chose to prepare, through a three-step protocol, bicyclic oxazocinediones (Scheme 3). The diastereomeric mixture of **14** and **15a** was treated with HF to give alcohols **16** and **17**, which were separated and individually transformed into the corresponding hydroxyacids by hydrogenolysis and then cyclized by means of PyBOP [(benzotriazolyl-1-oxy)tripyrrolidinophosphonium hexafluorophosphate] as condensing agent under high dilution conditions.



Scheme 3. (a) HF, CH_3CN, 0 °C; (b) (i) H_2, Pd/C, EtOH, rt; (ii) PyBOP, Et_3N, CH_2Cl_2 2 mM, reflux.

The diversity that can be achieved by coupling the MCR with a secondary transformation is not only limited to the 'scaffold diversity', but also can be finely tuned from a stereochemical point of view. Actually, the absolute configuration of **13** can be decided by choosing L- or D-glutamic acid as starting material, whereas the configuration of the aspartic acid derivative can be decided at will as well. On the other hand, the third stereogenic center is generated during the Ugi condensation. The moderate stereoselectivity was not therefore a drawback because it allows to obtain two diastereomeric products. In order to increase the stereochemical diversity we synthesized also **14** and **15b**, employing Boc-D-Asp(OBn) and submitted the deprotected alcohols **18** and **19** to the above described protocol. Compound **23**, coming from **15b**, was obtained, although in less satisfactory yield, while its epimer **22** was never isolated. We do not have a rational explanation for this behavior, even if it is clear that the spatial position of the NHBoc must prevent the formation of the eight-membered heterocycle. A problem related to structures **20**, **21**, and **23** is represented by the presence of the lactone, a functional group not always appropriate for pharmacological applications, due to potential hydrolytic lability. So we focused our attention to the preparation of more stable compounds.[28]

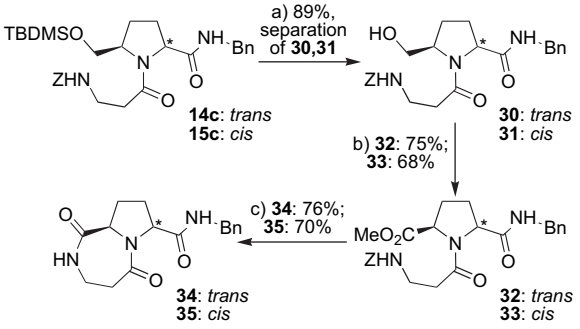
We reasoned that **16** and **17** could be exploited as common intermediates to prepare *N*-derivatives, such as diazocinediones **26** and **27** (cyclic hydroxamic acids) or **28** and **29** (lactams). The latters are in principle accessible from the formers by reductive cleavage of the N–O bond (Scheme 4). However, as recently reported elsewhere,[13] we were unable to obtain **26** and **27** by cyclization of the hydroxy hydroxamate under Mitsunobu's conditions. For this reason we turned our attention to a different protocol, planning to replace the hydroxy group with a primary amino group to be used only for the formation of the lactam ring. The nucleophilic displacement of the mesylate of **16** or **17** by means of sodium azide occurred but surprisingly with epimerization at the neighboring stereocenter. Starting from **16**, we always isolated a ≈1:1 mixture of diastereomeric products **24**; the same happened starting from the cis counterpart **17**. Epimers **24** showed different chromatographic and spectroscopic properties, compared to products **25** derived from **17**. This outcome demonstrates that epimerization had involved the stereogenic center near to the azide, probably as the result of a non-stereoselective elimination–addition process. This prompted us to explore a different strategy.



Scheme 4. (a) (i) MsCl, Et_3N, CH_2Cl_2, −30 °C; (ii) NaN_3, DMF, 50 °C.

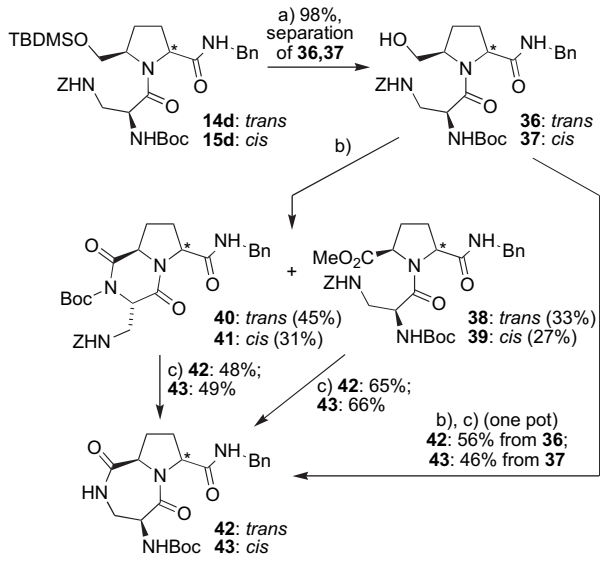
In particular, knowing that the hydroxymethyl group can be easily oxidized, without epimerization, by the Jones reagent to the carboxylic moiety,[14] we reasoned that the above mentioned epimerization could have been circumvented by inverting the position of the carboxylic moiety and the amino group, as illustrated in Scheme 5. First simple commercially available Z-β-alanine was used as carboxylic input to give **14** and **15c**. Initial attempts to cyclize the aminoacid, obtained by

removal of TBDMS, oxidation of the primary alcohols **30** and **31**,[29] and deprotection of the amine, with typical condensing agents used in peptide chemistry such as PyBOP, BOP, etc., failed. At the end **34** and **35** were successfully prepared by refluxing the amino ester, obtained by removing the Z group from **32** and **33**, in ^{t}BuOH in the presence of triethylamine.[15,30] This time crucial high dilution conditions (used, for example, for the preparation of **20**, **21**, and **23**) were unnecessary for obtaining the seven-membered ring.



Scheme 5. (a) HF, MeCN, rt; (b) (i) Jones oxidation, Me_2CO, 0 °C; (ii) CH_2N_2, THF, 0 °C; (c) (i) H_2, Pd/C, MeOH, rt; (ii) ^{t}BuOH, Et_3N, 0.2 M, reflux.

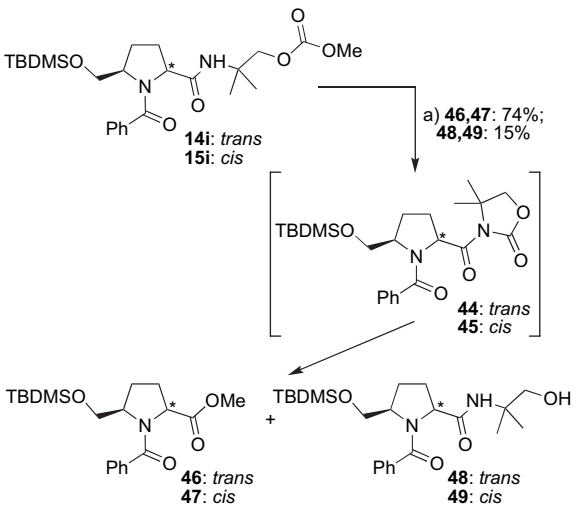
Encouraged by this result we extended our protocol to compounds **14** and **15d**, having two orthogonally protected primary amines (Scheme 6). Actually, the additional amino group represents an important feature, since it can be used as a handle to improve the molecular complexity of the final scaffold. We were quite surprised when we noticed the formation in comparable amount of two compounds during the oxidation step, either starting from **36** or **37**. We recognized the slightly prevailing products as the desired methyl esters **38** and **39**, and we assigned to the others the structure of the diketopiperazines of formula **40** and **41**. These compounds themselves represent an interesting new scaffold, belonging to a class of



Scheme 6. (a) HF, MeCN, 0 °C; (b) (i) Jones oxidation, Me_2CO, 0 °C; (ii) CH_2N_2, THF, 0 °C; (c) (i) H_2, Pd/C, MeOH, rt; (ii) ^{t}BuOH, Et_3N, 0.2 M, reflux.

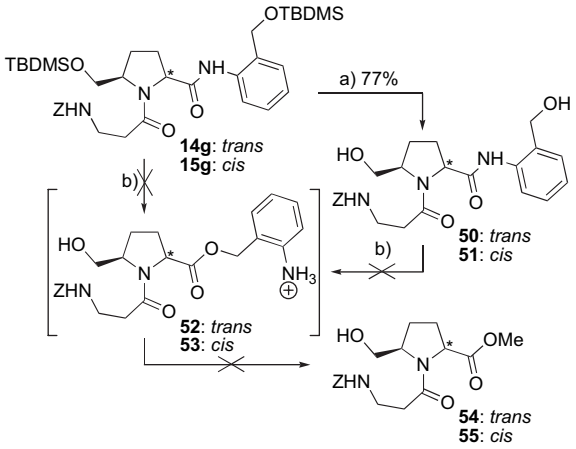
heterocycles that has been widely investigated in combinatorial synthesis, by combining MCRs with secondary transformations.[5,31–33] Moreover, we found that both **38**, **39** and **40**, **41** can be conveniently transformed into the final diazepinediones **42** and **43**, under the same conditions, respectively, by intramolecular aminolysis of an ester and of an imide. Thus it was not necessary to separate **38** from **40** or **39** from **41**: actually, when the mixture of **38** and **40** or of **39** and **41** was independently submitted to the hydrogenolysis–cyclization protocol, the desired **42** and **43** were obtained with an even higher overall yield!

Another possibility for gaining access to this kind of scaffolds is a cyclization involving the side arm coming from the isocyanide. By this way the protected hydroxymethyl group remains available as a handle, allowing further diversity generation, by joining to it peptidomimetic substructures. Of course a traditional secondary amide is unsuitable for this strategy and so we studied the utilization of a so-called 'convertible isocyanide', choosing first the carbonate introduced by Ugi.[24] For preliminary optimization studies we employed model compounds **14** and **15i** (Scheme 7). The secondary amide, generated by the attack of the isocyanide to pyrroline **13**, can in principle be converted into the acyl oxazolidinones **44** and **45**, by treatment with an alkoxide (^{t}BuOK in the original paper). Methoxide, delivered during the cyclization, is then responsible for the acylic nucleophilic displacement on activated **44** and **45** to give methyl esters **46** and **47**. In our hands the Ugi protocol, which has been used only in few cases until now,[33,34] did not work as well as expected. The desired **46** and **47** turned out to be only the minor products (29%), while the prevailing ones were useless alcohols **48** and **49** (38%). So we undertook a careful tuning of the reaction conditions. We found that the formation of the primary alcohol is independent from the presence of traces of water.[35] The best base turned out to be sodium methoxide, whereas the best carbonate was the methyl one and rt was better than higher or lower temperatures. Finally, the work-up of choice involved the introduction of 10% aqueous citric acid in the reaction mixture.



Scheme 7. (a) MeONa, MeOH, rt.

Although the suppression of undesired **48** and **49** was never possible on this family of compounds, we finally obtained an acceptable 74% yield of **46** and **47**.[36] We were, however, very concerned when we noticed that this protocol was not well suited for more functionalized Ugi products, such as, for example, **14**, **15e** and **14**, **15f**. For this reason we turned our attention to a different removable isocyanide, as summarized in Scheme 8.

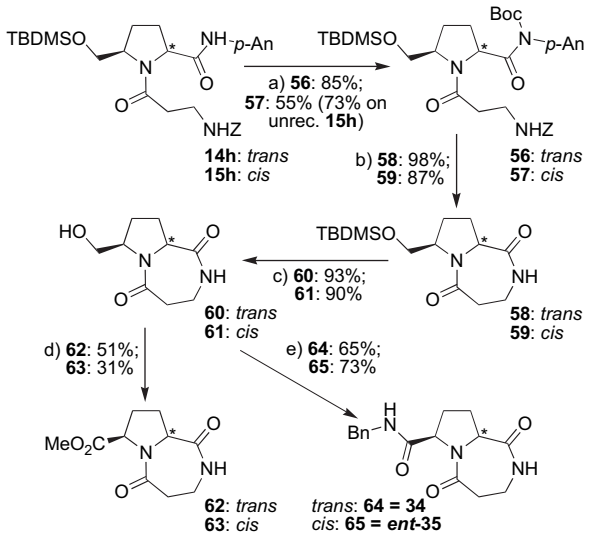


Scheme 8. (a) HF, MeCN, 0 °C; (b) concd HCl, MeOH, rt.

The transformation of the secondary amide coming from the isocyanide into the corresponding methyl ester represents an example of the unusual nitrogen to oxygen migration of an acyl group, where the equilibrium is probably driven by the acid conditions leading to the protonated intermediates **52** and **53**.[25] Since, in the route from **14** and **15g** to **54** and **55**, several reactions must occur, we preferred first to deprotect the alcohols and then submit **50** and **51** to the migration, having in mind to test the one-pot procedure only later. Whatever the reaction conditions we never succeeded in isolating the desired esters **54** and **55**, identifying instead the methyl ester of Z-β-alanine. The high lability of the tertiary amide is probably enhanced by the presence of the free hydroxymethyl group, which assists the cleavage of the N–CO bond, as previously observed also by Evans.[37]

We finally turned our attention to the use of an isocyanide, which gives a secondary amide that can be further activated in order to undergo an intramolecular transamidation reaction promoted by the primary amine (Scheme 9), not requiring therefore the preparation of the methyl ester. A similar strategy has been previously adopted in the synthesis of pyrroles on solid phase[38] and for cleaving Ugi products from a solid support.[32]

On our compounds this strategy gave excellent results on the *trans*-**14h** derivative. Actually, the activation of the aromatic secondary amide was achieved by introducing a Boc group. This transformation was not trivial, due to the competition of the NHZ group: only after a careful optimization of the reaction conditions we obtained **56** in excellent yield. The same did not happen with **15h**: on this stereoisomer the regioselectivity was not so marked and the reaction was rather



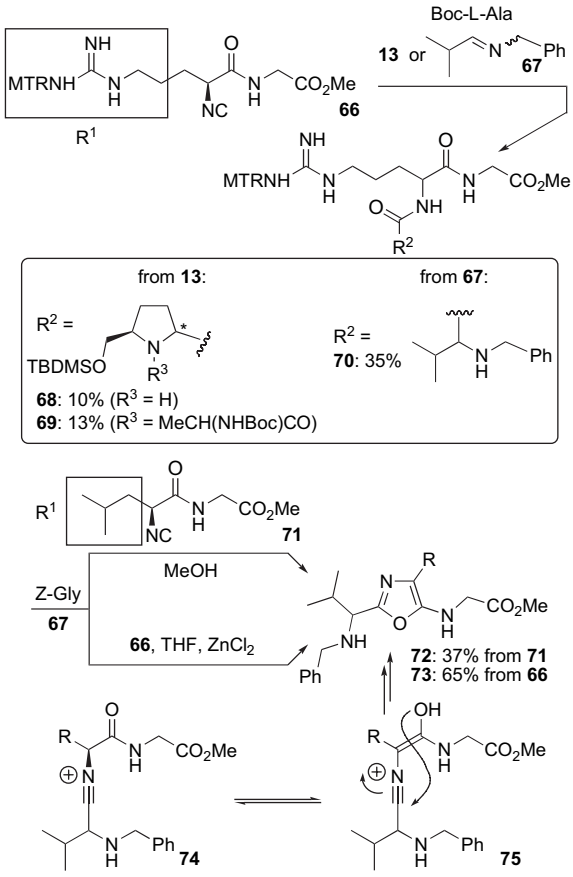
Scheme 9. (a) Boc_2O, Et_3N, DMAP, CH_2Cl_2, rt; (b) (i) H_2, Pd/C, MeOH, rt; (ii) ^{t}BuOH, 0.2 M, reflux; (c) Amberlyst 15, MeOH, rt; (d) (i) PDC, DMF, rt; (ii) CH_2N_2, DMF, 0 °C; (e) (i) PDC, DMF, rt; (ii) $PhCH_2NH_2$, HATU, 2,4,6-collidine, DMF/CH_2Cl_2, rt.

slow and we never succeeded to achieve complete conversion of the starting material. Probably, the relative position of the substituents on **15h** caused such a steric hindrance that partially prevented approaching of the reagent and so competition of the less reactive NHZ group became more important. Moreover **57** was difficult to separate from its isomer bearing the N(Boc)Z moiety instead of N(Boc)*p*-An. Anyway the following nucleophilic displacement, by the free amino group, gave excellent results affording diastereomeric compounds **58** and **59**. The protected hydroxymethyl group can be exploited for further elaborations. We, for example, succeeded in converting it into amides. Removal of TBDMS was not performed under the usual conditions, due to the noticeable insolubility of **60** and **61** in any organic solvent and the great affinity for water, which prevented an extractive work-up. This problem was solved employing Amberlyst 15, which was easily removed by filtration together with $CaCO_3$ used for eliminating the residual acidity. The insolubility prevented also the employment of Jones oxidation. Under optimized conditions we performed the oxidation with pyridinium dichromate in DMF. After reducing the excess of oxidant by addition of solid sodium metabisulphite, the crude product was filtered on a silica gel column to remove Cr derivatives, and the resulting acid was directly coupled with benzylamine or treated with diazomethane, always in DMF. The overall moderate yield of methyl esters **62** and **63** is probably a consequence of employing unavoidable DMF as solvent. Since coupling of the acid with benzylamine gave good results, the responsibility cannot be attributed to the oxidative step. Probably the yield of methylation may be improved using methods alternative to CH_2N_2 such as a coupling under the same conditions used to prepare **64** and **65**. Anyway, the efficient transformation of **60** and **61** into **64** and **65** discloses the possibility to introduce by the same protocol a series of different nitrogen derivatives.

Moreover, compounds **64** and **65** gave us also the possibility to unequivocally confirm the relative stereochemistry of the major part of the scaffolds prepared. Actually, bicyclic derivatives coming from Ugi adducts with trans substituents, prepared either following procedure of Scheme 5 or 9, have to be identical for symmetry reasons, while the analogous with cis substituents have to be enantiomers. In our hand, scaffolds **34** and **64** showed the following values of $[\alpha]_D$ +38.4 and +37.3, while compounds **35** and **65** gave: +28.1 and −25.1, respectively, thus confirming our hypothesis.

The strategy used for preparing scaffolds **64** and **65** may be useful, since it offers a real possibility to bind to the pyrrolidine nucleus a primary amine (also derived form an amino acid or a peptide), producing a secondary amide. Although the same products could be in principle prepared in a more convergent way starting from a suitable isocyanide and following therefore the strategy described in Schemes 5 and 6, it should be stressed that peptide or amino ester derived isocyanides cannot be utilized in the Ugi reaction (instead of benzylisocyanide used to prepare **14**, **15c** and **14**, **15d**). When we attempted to do so, we experienced many troubles. With isocyanides synthesized from simple chiral α-amino acid esters the Ugi reaction gave the desired products, but with complete racemization at the carbon bearing the resulting secondary amide.[39] When the Ugi reaction was performed with isocyanides derived from dipeptides we observed a sluggish reaction with the formation of many products. Some of them have been isolated in modest yield and have been identified (a few examples are illustrated in Scheme 10). Using isocyanide **66** with an arginine derived appendage, we noticed that the carboxylic input is not (or only in part) included into the products and this behavior do not depend upon the structure of the imine. When the arginine was replaced by an unfunctionalized residue (**71**) a heterocycle such as **72** was isolated. Interestingly the same type of compound (**73**) was also isolated when isocyanide **66** was reacted under non-conventional Ugi conditions.[41]

Recently 5-aminooxazoles such as **72** and **73** have been isolated when a tertiary α-isocyanoacetamide (that is, with a $CONR_2$ group on the carbon α to the NC group) is reacted with an amine and a carbonyl compound.[40] However, the same behavior has never been reported before with peptide-derived isocyanides where the α-isocyanoacetamide is secondary. The formation of these unexpected products can be explained by the fact that iminium ion **74**, one of the intermediates of the reaction that is in equilibrium with its tautomer **75**, undergoes an intramolecular nucleophilic attack by the hydroxy group, instead of reacting with the carboxylate in an intermolecular fashion. Interestingly, when arginine derived isocyanide **66** was employed, the intramolecular attack was probably promoted this time by a nitrogen atom of the guanidine moiety, to give a cyclic adduct that was opened during work-up to give **68** or **70** but in both cases the carboxylic moiety was not incorporated in the final product. The unexpected and most of all unpredictable reactivity of these isocyanides when submitted to Ugi protocol showed clearly that they are unsuitable inputs for these MCRs.



Scheme 10. Ugi reaction outcome with isocyanides derived from dipeptides.

3. Conclusions

In this paper we presented a series of secondary transformations that can be coupled with an efficient and very convergent Ugi reaction. By this protocol we opened the way to a series of unknown or nearly unknown bicyclic heterocycles. The same strategy can of course be extended also to more functionalized systems in order to increase the diversity and to offer the possibility to decorate them with groups of interest for interactions with biological targets, such as, for example, integrins.

4. Experimental

4.1. General

NMR spectra were taken (at rt if not otherwise indicated) in $CDCl_3$ or DMSO-d_6 at 200 or 300 MHz (^{1}H) and 50 or 75 MHz (^{13}C), using TMS as internal standard for $CDCl_3$ spectra. The solvent is specified only for ^{1}H NMR, meaning that the same was used also for ^{13}C NMR. Chemical shifts are reported in parts per million (δ scale), coupling constants are reported in hertz. Peak assignment in ^{1}H NMR spectra was also made with the aid of double resonance experiments, gCOSY, and NOESY experiments (bicyclic compounds). In AB and ABX systems the proton A is considered downfiled

and B upfield. Peak assignment in ^{13}C spectra was made with the aid of DEPT and gHSQC experiments. In many compounds a mixture of rotamers can be identified; therefore different signals, which can be attributed to the rotamers, are identified as *M* (major) and *m* (minor). Unless otherwise indicated spectra were recorded at rt. GC–MS were carried out on a HP-5971A instrument, using an HP-1 column (12 m long, 0.2 mm wide), electron impact at 70 eV, and a mass temp of about 170 °C. Unless otherwise indicated analyses were performed with a constant He flow of 0.9 ml/min, init. temp=100 °C, init. time=2 min, rate=20 °C/min, final temp=260 °C, final time=4 min, inj. temp=250 °C, det. temp=280 °C. t_R are in minutes. HPLC determinations were carried out on a HP-1090 instrument equipped with DAD. Columns and conditions are reported in the appropriate section. HPLC–MS experiments of compounds **42** and **43** were carried out on an HP-1100 (column Synergi Hydro 150×3 mm, 4 μm; $H_2O{\cdot}CH_3CO_2H$ (0.2%)/CH_3CN 30:70, flow 0.5 ml/min, temp=35 °C, equipped with an Agilent Ion Trap, source ESI, nebulizer=30 psi, dry=10 l/min, temp=300 °C, HV capillary=3200 V, mass range=50–1300, collision energy=2 V. IR spectra were measured with a Perkin–Elmer 881 instrument as $CHCl_3$ solutions, unless otherwise indicated, and absorptions are reported in cm^{-1}. Melting points were determined on a Büchi 535 apparatus and are uncorrected. Values of $[\alpha]_D$ were determined on a Jasco DIP 181 polarimeter, in $CHCl_3$ (containing 0.75–1% EtOH) solution, unless otherwise indicated. TLC analyses were carried out on silica gel plates, which were developed by these detection methods: (**A**) UV; (**B**) iodine; (**C**) dipping into a solution of $(NH_4)_4MoO_4{\cdot}4H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4H_2O$ (1 g) in H_2SO_4 (31 ml) and H_2O (469 ml) and warming; (**D**) dipping into a solution of ninhydrin (900 mg), *n*-butanol (300 ml), and AcOH (9 ml) and warming. R_f were measured after an elution of 7–9 cm. Chromatographies were carried out on 220–400 mesh silica gel using the 'flash' methodology. Petroleum ether (40–60 °C) is abbreviated as PE. In extractive work-up, aqueous solutions were always re-extracted thrice with the appropriate organic solvent. Organic extracts were washed with brine, dried over Na_2SO_4, and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen atmosphere.

4.2. 3-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)prop-1-yl acetate ***7***

A solution of **6** (15.18 g, 94.75 mmol) in dry pyridine (40 ml) was treated with acetic anhydride (13.4 ml, 142.16 mmol) and stirred at rt for 1.75 h. The solution was partitioned between water and Et_2O and extracted. The combined organic layers were dried and the solvent was evaporated. Residue pyridine was azeotropically removed with heptane. The crude was purified by chromatography with PE/Et_2O 100:0→1:1 to give **7** (18.40 g, 96%) as a pale yellow oil. R_f 0.36 (PE/Et_2O 6:4, **C**). Anal. Found: C, 59.50; H, 8.85. $C_{10}H_{18}O_4$ requires C, 59.39; H, 8.97. $[\alpha]_D^{20}$ +13.2 (*c* 1.08). IR: ν_{max} 2981, 1727, 1370, 1191, and 1044. GC–MS: t_R 4.91; *m/z* 187 (M^+, 29), 145 (11), 127 (5.8), 101 (8.6), 85 (26), 73 (6.7), 72 (24), 67 (48), 59 (7.3), 57 (5.0), 55 (5.9), 43 (100), 42 (11), 41 (11), 39 (7.7). ^1H NMR (200 MHz, $CDCl_3$): 1.35 and 1.41 [6H, 2s, $C(CH_3)_2$]; 1.55–1.83 [4H, m, $(CH_2)_2CH_2OAc$]; 2.05 [3H, s, $COCH_3$]; 3.52 [1H, center of m, C*H*O]; 4.01–4.17 [4H, m, CH_2O]. ^{13}C NMR (50 MHz): 20.8 [CH_3CO]; 24.9 and 25.6 [2C, $C(CH_3)_2$]; 26.8 [CH_2CH_2OAc]; 30.0 [$CH_2(CH_2)_2OAc$]; 64.1 [CH_2OAc]; 69.2 [$CHCH_2O$]; 75.4 [*C*H]; 108.8 [$C(CH_3)_2$]; 170.9 [*C*O].

4.3. (S)-4,5-Dihydroxypent-1-yl acetate ***8***

A solution of **7** (18.40 g, 14.75 mmol) in water (330 ml) was diluted with acetic acid (150 ml) and stirred at rt for 5 h. The solvent was evaporated in vacuo and acetic acid was azeotropically removed with heptane. The crude was purified by chromatography with AcOH/MeOH 100:0→96:4 to give **8** (14.75 g, 100%) as a pale yellow oil. R_f 0.34 (AcOEt/MeOH 98:2, **C**). Anal. Found: C, 52.05; H, 8.60. $C_7H_{14}O_4$ requires C, 51.84; H, 8.70. $[\alpha]_D^{20}$ +2.9 (*c* 2.04). IR: ν_{max} 3585, 3445, 2949, 1726, 1365, 1193, and 1030. GC–MS (usual method but starting from 80 °C): t_R 5.05; *m/z* 132 (M^+–40, 0.78), 71 (100), 61 (23), 57 (5.6), 44 (6.2), 43 (87), 42 (8.7), 41 (12). ^1H NMR (200 MHz, $CDCl_3$): 1.41–1.94 [4H, m, $(CH_2)_2CH_2OAc$]; 2.05 [3H, s, $COCH_3$]; 3.46 and 3.67 [2H, AB part of an ABX system, CH_2OH, J_{AB}=11.2, J_{AX}=7.2, J_{BX}=2.3]; 3.74–3.80 [1H, m, C*H*O]; 4.12 [2H, t, CH_2OAc, *J*=6.4]. ^{13}C NMR (50 MHz): 20.9 [CH_3CO]; 24.7 [CH_2CH_2OAc]; 29.2 [$CH_2(CH_2)_2OAc$]; 64.3 [CH_2OAc]; 66.5 [$CHCH_2O$]; 71.6 [*C*H]; 171.4 [*C*O].

4.4. (S)-5-[(tert-Butyldimethylsilyl)oxy]-4-hydroxypent-1-yl acetate ***9***

A solution of **8** (8.51 g, 52.47 mmol) in dry THF (100 ml) was treated with imidazole (8.30 g, 55.10 mmol) and 4-dimethylamino pyridine (96 mg, 78.58 μmol) and then cooled to 0 °C. A solution of *tert*-butyldimethylsilyl chloride (TBDMS-Cl, 8.31 g, 55.13 mmol) in dry THF (50 ml) was added via syringe. After 2 h the reaction was stirred at rt for 3 h. In some cases an addition of the reagents (TBDMS-Cl and imidazole, 0.1 molar equivalents) was required to have complete reaction of the substrate. After addition of water (15 ml) the solution was partially concentrated in vacuo and then partitioned between water and Et_2O, and extracted. The combined organic layers were dried and the solvent was evaporated. The crude was purified by chromatography with PE/Et_2O 9:1→4:6 to give **9** (13.93 g, 96%) as a pale yellow oil. R_f 0.44 (PE/Et_2O 1:1, **C**). Anal. Found: C, 56.65; H, 10.35. $C_{13}H_{28}O_4Si$ requires C, 56.48; H, 10.21. $[\alpha]_D^{20}$ +2.8 (*c* 2.98). IR: ν_{max} 2950, 2926, 1726, 1364, 1193, 1091, and 832. GC–MS: t_R 6.15; *m/z* 219 (M^+–57, 0.10), 160 (7.5), 159 (57), 141 (9.2), 131 (9.2), 117 (29), 105 (9.1), 103 (6.0), 89 (12), 85 (21), 77 (11), 76 (7.8), 75 (100), 73 (30), 71 (14), 67 (26), 61 (7.2), 59 (9.2), 58 (5.6), 57 (8.6), 55 (5.3), 47 (6.0), 45 (9.0), 43 (60), 41 (10). ^1H NMR (200 MHz, $CDCl_3$): 0.08 [6H, s, $Si(CH_3)_2$]; 0.91 [9H, s, $C(CH_3)_3$]; 1.41–1.95 [4H, m, $(CH_2)_2CH_2OAc$]; 2.05

[3H, s, COCH_3]; 2.46 [1H, br d, OH, J=3.0]; 3.41 and 3.63 [2H, AB part of an ABX system, CH_2OH, J_{AB}=10.3, J_{AX}=7.9, J_{BX}=2.8]; 3.62–3.73 [1H, m, CHO]; 4.10 [2H, t, CH_2OAc, J=6.4]. ^{13}C NMR (50 MHz): −5.48 and −5.44 [2C, Si(CH_3)$_2$]; 18.2 [C(CH$_3$)$_3$]; 20.9 [CH_3CO]; 24.8 [CH_2CH_2OAc]; 25.8 [3C, C(CH_3)$_3$]; 29.1 [CH_2(CH$_2$)$_2$OAc]; 64.4 [CH_2OAc]; 67.1 [CH_2OSi]; 71.3 [CH]; 171.1 [CO].

4.5. Mosher's esters (MTPA esters) of **9**

A solution of **9** (5.0 mg, 18.09 μmol) in dry CH_2Cl_2 (500 μl) was cooled to 0 °C and treated with 4-dimethylamino pyridine (14 mg, 108.52 μmol) and MTPA-Cl (10 μl, 54.26 μmol, either *R*- or *S*-chloride). After 10 min the reaction was stirred at rt for 50 min. The crude was directly purified by preparative PLC to give the desired MTPA esters in 85–90% yield. R_f 0.77 (PE/Et$_2$O 1:1, **A** and **C**). Selected ^{1}H NMR data showing the differences between the diastereomeric esters (200 MHz, $CDCl_3$): (a) *S*,*R* ester from *S*-MTPA-Cl: 3.53 [3H, q, OCH_3, J=1.0]; 3.63 and 3.69 [2H, AB part of an ABX system, CH_2OSi, J_{AB}=10.9, J_{AX}=4.5, J_{BX}=5.7]; 4.06 [2H, br t, CH_2OAc, J=5.8]; 5.13 [1H, center of m, CHOCO]; (b) *S*,*S* ester from *R*-MTPA-Cl: 3.59 [3H, q, OCH_3, J=1.2]; 3.73 [2H, apparent d, CH_2OSi, J=5.0]; 3.98 [2H, br t, CH_2OAc, J=6.0]; 5.17 [1H, br quintuplet, CHOCO, J=5.6].

4.6. (R)-4-Azido-5-{[(tert-butyldimethylsilyl)oxy]pentyl} acetate **10**

(a) Mesylate: a solution of **9** (13.93 g, 50.39 mmol) in dry CH_2Cl_2 (150 ml) was cooled to −30 °C and treated with Et_3N (9.1 ml, 65.51 mmol) and MsCl (4.7 ml, 60.47 mmol). After 1 h the reaction was quenched with NH_4Cl (aq saturated solution), diluted with water to dissolve all the solid and extracted with Et_2O. After drying and solvent removal, crude mesylate was used as such in the following reaction. R_f 0.48 (PE/Et$_2$O/CH_2Cl_2 45:10:45, **C**). (b) Substitution with NaN_3: to a solution of crude mesylate in dry DMF (60 ml) was added sodium azide (6.56 g, 100.91 mmol) and the suspension was stirred at 65 °C for 6 h. The crude was partitioned between water and Et_2O, and extracted. The combined organic layers were dried and the solvent was evaporated. The crude was purified by chromatography with PE/Et$_2$O 95:5→8:2 to give **10** (13.67 g, 90%) as a pale yellow oil. R_f 0.82 (PE/Et$_2$O/CH_2Cl_2 45:10:45, **C**). Anal. Found: C, 51.95; H, 9.15; N, 13.80. $C_{13}H_{27}N_3O_3Si$ requires C, 51.79; H, 9.03; N, 13.94. $[\alpha]_D^{20}$ +25.4 (*c* 2.59). IR: ν_{max} 2952, 2926, 2104, 1727, 1249, 1113, 1047, and 831. GC–MS: t_R 6.66; *m*/*z* 273 (M^+−28, 0.087), 159 (5.8), 157 (8.0), 156 (34), 141 (7.5), 130 (9.8), 128 (22), 118 (8.1), 117 (78), 116 (7.4), 115 (17), 114 (5.9), 101 (7.4), 100 (19), 89 (27), 88 (11), 86 (5.6), 85 (5.6), 82 (5.5), 76 (5.4), 75 (66), 73 (66), 67 (11), 61 (6.5), 59 (22), 58 (18), 57 (12), 55 (6.2), 47 (5.6), 45 (15), 43 (100), 42 (7.1), 41 (21), 39 (5.3). ^{1}H NMR (200 MHz, $CDCl_3$): 0.09 [6H, s, Si(CH_3)$_2$]; 0.91 [9H, s, C(CH_3)$_3$]; 1.38–1.92 [4H, m, (CH_2)$_2$CH$_2$OAc]; 2.05 [3H, s, COCH_3]; 3.31–3.40 [1H, m, CHN$_3$]; 3.63 and 3.73 [2H, AB part of an ABX system, CH_2OSi, J_{AB}=10.3, J_{AX}=6.8, J_{BX}=4.0]; 4.09 [2H, t, CH_2OAc, J=6.4]. ^{13}C NMR (50 MHz): −5.6 [2C, Si(CH_3)$_2$]; 18.1 [C(CH$_3$)$_3$]; 20.8 [CH_3CO]; 25.3 [CH_2CH_2OAc]; 25.7 [3C, C(CH_3)$_3$]; 26.9 [CH_2(CH$_2$)$_2$OAc]; 63.2 [CH]; 63.9 [CH_2OAc]; 66.2 [CH_2OSi]; 171.0 [CO].

4.7. (R)-4-Azido-5-{[(tert-butyldimethylsilyl)-oxy]pentan}-1-ol **11**

A solution of **10** (13.67 g, 45.35 mmol) in MeOH (68 ml) was cooled to 0 °C and treated with KOH (1 M solution in MeOH, 68 ml). After 45 min the reaction was quenched with NH_4Cl (aq saturated solution) and concentrated in vacuo. The residue was extracted with Et_2O. The combined organic layers were dried and the solvent was evaporated. The crude was purified by chromatography with PE/Et$_2$O 8:2→4:6 to give **11** (11.53 g, 98%) as a pale yellow oil. R_f 0.45 (PE/Et$_2$O 1:1, **C**). Anal. Found: C, 51.15; H, 9.55; N, 16.30. $C_{11}H_{25}N_3O_2Si$ requires C, 50.93; H, 9.71; N, 16.20. $[\alpha]_D^{20}$ +26.7 (*c* 1.95). IR: ν_{max} 3454, 2987, 2108, 1708, 1191, 1114, and 833. GC–MS: t_R 6.03; *m*/*z* 202 (M^+−57, 0.14), 159 (18), 156 (6.6), 144 (8.5), 141 (11), 131 (7.6), 130 (40), 129 (7.1), 128 (10), 127 (12), 116 (5.6), 115 (8.7), 114 (5.1), 101 (9.9), 100 (19), 89 (24), 88 (8.6), 86 (6.3), 85 (6.2), 77 (5.2), 76 (7.9), 75 (100), 74 (11), 73 (50), 70 (9.1), 59 (17), 58 (13), 57 (8.6), 55 (5.9), 45 (8.8), 43 (8.4), 41 (10). ^{1}H NMR (200 MHz, $CDCl_3$): 0.09 [6H, s, Si(CH_3)$_2$]; 0.91 [9H, s, C(CH_3)$_3$]; 1.37–1.82 [4H, m, (CH_2)$_2$CH$_2$OH]; 3.33–3.45 [1H, m, CHN$_3$]; 3.59–3.79 [4H, m, CH_2O]. ^{13}C NMR (50 MHz): −5.6 [2C, Si(CH_3)$_2$]; 18.2 [C(CH$_3$)$_3$]; 25.7 [3C, C(CH_3)$_3$]; 26.6 [CH_2CH_2OH]; 29.1 [CH_2(CH$_2$)$_2$OAc]; 62.2 [CH_2OH]; 63.5 [CH]; 66.4 [CH_2OSi].

4.8. (R)-4-Azido-5-[(tert-butyldimethylsilyl)oxy]-pentanal **12**

To a solution of oxalyl chloride (31.3 ml, 66.67 mmol, 2.13 M solution in CH_2Cl_2) in dry CH_2Cl_2 (80 ml), previously cooled to −78 °C, dry DMSO (7.6 ml, 106.67 mmol) was added. After 10 min stirring a solution of **12** (11.53 g, 44.45 mmol) in dry CH_2Cl_2 (40 ml) was added followed, after 10 min, by Et_3N (26 ml, 186.67 mmol). After 2 h the reaction was quenched with NH_4Cl (aq saturated solution) and extracted with Et_2O. The combined organic layers were dried and the solvent was evaporated. The crude was purified by chromatography with PE/Et$_2$O 75:25→1:1 to give **12** (10.07 g, 88%) as a pale yellow oil. R_f 0.72 (PE/Et$_2$O 1:1, **C**). Anal. Found: C, 51.35; H, 9.15; N, 16.25. $C_{11}H_{25}N_3O_2Si$ requires C, 51.33; H, 9.01; N, 16.32. $[\alpha]_D^{20}$ +39.8 (*c* 2.10). IR: ν_{max} 2952, 2927, 2856, 2738, 2388, 2111, 1722, 1252, 1118, and 833. GC–MS: t_R 5.48; *m*/*z* 199 (M^+−58, 0.35), 157 (19), 156 (9.7), 154 (5.3), 143 (5.5), 142 (42), 129 (5.7), 128 (26), 127 (6.3), 116 (18), 115 (20), 101 (21), 100 (20), 99 (5.6), 89 (22), 88 (8.8), 84 (5.2), 76 (7.2), 75 (100), 74 (7.5), 73 (50), 59 (21), 58 (12), 57 (8.1), 45 (8.8), 43 (7.4), 41 (8.1). ^{1}H NMR (200 MHz, $CDCl_3$): 0.09 [6H, s, Si(CH_3)$_2$]; 0.91 [9H, s, C(CH_3)$_3$]; 1.63–1.94 [2H, m, CH_2CHO]; 2.61 [2H, br t, CH_2CH_2CHO, J=7.2]; 3.36–3.48 [1H, m, CHN$_3$]; 3.65 and 3.76 [2H, AB part of an ABX system,

CH_2OSi, J_{AB}=10.6, J_{AX}=6.9, J_{BX}=4.0]; 9.80 [1H, t, C*H*O, *J*=1.2]. ^{13}C NMR (50 MHz): −5.6 [2C, Si(*C*H$_3$)$_2$]; 18.1 [*C*(CH$_3$)$_3$]; 22.8 [*C*H$_2$CH$_2$CHO]; 25.7 [3C, C(*C*H$_3$)$_3$]; 40.3 [*C*H$_2$CHO]; 62.7 [*C*H]; 66.3 [*C*H$_2$OSi]; 201.1 [*C*O].

4.9. (R)-2-{[(tert-Butyldimethylsilyl)oxy]methyl}-3,4-dihydro-2H-pyrrol **13**

To a solution of **12** (6.94 g, 26.96 mmol) in dry THF (60 ml) freshly activated 4 Å powdered molecular sieves (520 mg) were added. After stirring for 15 min at rt, PPh_3 (8.49 g, 32.35 mmol) was added portionwise. After evolution of nitrogen finished, the reaction was stirred at 50 °C for 5 h. The sieves were filtered and the resulting solution was concentrated and directly purified by chromatography with PE/Et_2O 1:1→3:7 to give **13** (5.12 g, 89%) as a pale yellow oil.[20] R_f 0.52 (PE/Et_2O 2:8, **A** and **C**). Anal. Found: C, 61.80; H, 10.80; N, 6.70. $C_{11}H_{23}NOSi$ requires C, 61.91; H, 10.86; N, 6.56. $[\alpha]_D^{20}$ −73.3 (*c* 1.98, CH_2Cl_2). IR: ν_{max} 2951, 2928, 2855, 1190, 1113, and 717. GC−MS: t_R 3.77; *m/z* 213 (M^+, 0.12), 198 (5.5), 158 (8.5), 157 (28), 156 (100), 154 (8.3), 100 (6.0), 89 (21), 82 (5.3), 75 (34), 73 (41), 59 (19), 58 (7.9), 57 (5.3), 55 (8.1), 47 (8.1), 45 (13), 43 (8.0), 41 (17), 39 (8.1). ^{1}H NMR (200 MHz, $CDCl_3$): 0.04 and 0.06 [6H, 2s, Si(C*H*$_3$)$_2$]; 0.88 [9H, s, C(C*H*$_3$)$_3$]; 1.56−2.64 [4H, m, C*H*$_2$C*H*$_2$]; 3.65 and 3.76 [2H, AB part of an ABX system, C*H*$_2$OSi, J_{AB}=10.2, J_{AX}=6.9, J_{BX}=4.0]; 4.12−4.23 [1H, m, C*H*CH$_2$O]; 7.61 [1H, br s, C*H*=N]. ^{13}C NMR (50 MHz): −5.42 and −5.37 [2C, Si(*C*H$_3$)$_2$]; 18.2 [*C*(CH$_3$)$_3$]; 23.0 [*C*H$_2$CH$_2$CHN]; 25.9 [3C, C(*C*H$_3$)$_3$]; 37.1 [*C*H$_2$CHN]; 65.7 [*C*H$_2$OSi]; 74.5 [*C*H]; 167.4 [*C*H=N].

4.10. General procedure for the Ugi reaction with **13**

A solution of **13** in dry MeOH (≈0.3 M) was treated with the appropriate carboxylic acid and isocyanide (1.1−1.2 M equiv). The solution was stirred at rt until complete [usually 1−2 h, but up to 5 h (entries 4−7, Table 1)] and then diluted with AcOEt. This solution was washed with $NaHCO_3$ (5% aqueous solution) and brine. After drying, the solvent was evaporated and the crude was directly chromatographed. We not always succeeded in the separation of the two diastereoisomers; this was, however, always possible on the corresponding alcohols. Therefore, for preparative purposes, we preferred to separate the diastereoisomers after TBDMS removal. Moreover, since pyrrolidines such as **14** and **15** and their derivatives are involved in several conformational equilibria, the NMR spectra are often very complex, even at 90−120 °C, and therefore not always a complete characterization was possible. On the contrary, in bicyclic derivatives, the conformational equilibria disappeared or were less crucial and the final compounds have been fully characterized.

4.10.1. Compounds **14** and **15a**

Chromatography with CH_2Cl_2/AcOEt 8:2→7:3+0.5% MeOH gave **14a** as a colorless gum and **15a** as a white foam in 85% overall yield. dr: 66:34 [HPLC: column Supelco LC18 250×4.6 mm, 5 μm, MeOH/H_2O 8:2, flow=1 ml/min, DAD 220, t_R 13.56 (**14a**) and 14.98 (**15a**) min]. Compound **14a**: R_f 0.40 (CH_2Cl_2/AcOEt 8:2+0.5% MeOH, **A** and **C**). $[\alpha]_D^{20}$ +28.7 (*c* 2.10). IR: ν_{max} 3425, 2951, 2926, 1727, 1649, 1245, 1157, and 1109. GC−MS: unsuitable for this analysis. ^{1}H NMR (200 MHz, DMSO-d_6, rt: 71:30 mixture of rotamers): −0.001 and 0.02 [6H, 2s, Si(C*H*$_3$)$_2$]; 0.84 and 0.85 [9H, 2s, SiC(C*H*$_3$)$_3$]; 1.33 and 1.35 [9H, s, OC(C*H*$_3$)$_3$]; 1.67−2.86 [6H, m, C*H*$_2$ pyrrolidine, C*H*$_2$CO$_2$Bn]; 3.23−4.88 [7H, m, C*H*$_2$Ph, C*H*$_2$OSi, 3C*H*]; 4.82 and 4.91 (*m*) [2H, AB system, OC*H*$_2$Ph, *J*=12.8]; 5.03 and 5.09 (*M*) [2H, AB system, OC*H*$_2$Ph, *J*=12.6]; 7.16−7.35 [11H, m, aromatics, N*H*Boc (at 100 °C: br s at 6.74)]; 8.11 (*m*) [1H, br t, N*H*CH$_2$Ph, *J*=5.3 (at 100 °C: br s at 7.82)]; 8.71 (*M*) [1H, br t, N*H*CH$_2$Ph, *J*=5.5 (at 100 °C: br s at 8.38)]. ^{13}C NMR (50 MHz): −5.7, −5.63, and −5.58 [2C, Si(*C*H$_3$)$_2$]; 17.8 [*C*(CH$_3$)$_3$]; 24.7 (*M*) and 26.7 (*m*), 27.0 (*m*) and 30.1 [2C, *C*H$_2$ pyrrolidine]; 25.6 (*m*) and 25.7 (*M*) [3C, SiC(*C*H$_3$)$_3$]; 28.0 [3C, OC(*C*H$_3$)$_3$]; 35.1 (*M*) and 36.1 (*m*) [*C*H$_2$CO$_2$Bn]; 41.8 (*m*) and 42.2 (*M*) [NH*C*H$_2$Ph]; 48.4 (*m*) and 48.8 (*M*) [*C*HNHBoc]; 58.3 (*m*) and 59.2 (*M*), 60.2 (*M*) and 60.4 (*m*) [2C, *C*H pyrrolidine]; 61.6 (*M*) and 63.5 (*m*), 65.3 (*M*) and 65.4 (*m*) [2C, *C*H$_2$O]; 78.0 (*M*) and 78.6 (*m*) [O*C*(CH$_3$)$_3$]; 126.5, 126.6, 126.7, 127.0, 127.5, 127.7, 127.8, 128.1, 128.15, and 128.22 [10C, aromatic *C*H]; 135.8 (*m*) and 136.0 (*M*), 138.9 (*M*) and 139.3 (*m*) [2C, aromatic *C*]; 155.0 (*M*) and 155.2 (*m*) [*C*O (Boc)]; 169.1, 169.9, 170.0, 170.4, 171.2, and 171.8 [3C, *C*O (amide, lactone)]. Compound **15a**: R_f 0.23 (CH_2Cl_2/AcOEt 8:2+0.5% MeOH, **A** and **C**). $[\alpha]_D^{20}$ −35.8 (*c* 3.14). IR: ν_{max} 3421, 3005, 2954, 1721, 1655, 1292, 1188, 1161, 1094, and 811. GC−MS: unsuitable for this analysis. ^{1}H NMR (200 MHz, DMSO-d_6, rt: 78:22 mixture of rotamers) at 100 °C: 0.03 [6H, s, Si(C*H*$_3$)$_2$]; 0.87 [9H, s, SiC(C*H*$_3$)$_3$]; 1.39 [9H, s, OC(C*H*$_3$)$_3$]; 1.82−2.21 [4H, m, C*H*$_2$ pyrrolidine]; 2.68 and 2.79 [2H, AB part of an ABX system, C*H*$_2$CO$_2$Bn, J_{AB}=16.4, J_{AX}=7.5, J_{BX}=6.2]; 3.52−4.75 [7H, m, C*H*$_2$Ph, C*H*$_2$OSi, 3C*H*]; 5.05 [2H, s, OC*H*$_2$Ph]; 6.85 [1H, br s, *NH*Boc (at rt: 2d at 7.10, *J*=7.6 and 7.48, *J*=7.2)]; 7.21−7.35 [10H, m, aromatics]; 7.83 [1H, br s, N*H*CH$_2$Ph (at rt: 2br s at 8.10 and 8.32)]. ^{13}C NMR (50 MHz): −5.7 and −5.6 [2C, Si(*C*H$_3$)$_2$]; 17.9 [*C*(CH$_3$)$_3$]; 25.7 [3C, SiC(*C*H$_3$)$_3$]; 26.7, 26.9, and 29.6 [2C, *C*H$_2$ pyrrolidine]; 28.0 [3C, OC(*C*H$_3$)$_3$]; 36.2 [*C*H$_2$CO$_2$Bn]; 41.8 (*M*) and 42.6 (*m*) [NH*C*H$_2$Ph]; 48.1 (*M*) and 49.2 (*m*) [*C*HNHBoc]; 58.9 (*M*) and 59.8 (*m*), 60.4 (*M*) and 61.0 (*m*) [2C, *C*H pyrrolidine]; 63.0 (*M*) and 63.6 (*m*), 65.5 [2C, *C*H$_2$O]; 78.4 (*M*) and 78.5 (*m*) [O*C*(CH$_3$)$_3$]; 126.5, 126.7, 127.0, 127.7, 127.9, 128.1, 128.2, and 128.3 [10C, aromatic *C*H]; 135.8, 139.0 (*m*), and 139.2 (*M*) [2C, aromatic *C*]; 155.0 [*C*O (Boc)]; 169.9, 170.1, 170.8, and 171.3 [3C, *C*O].

4.10.2. Compounds **14** and **15b**

Chromatography with PE/AcOEt 7:3→1:1+0.5% MeOH gave **14** and **15b** as an unseparable mixture (white foam) in 79% overall yield. dr: 62:38 by weight after chromatographic separation of the corresponding alcohols **18** and **19**. Compound **14b**: R_f 0.46 (PE/AcOEt 6:4+0.5% MeOH, **A** and **C**). Compound

15b: R_f 0.40 (PE/AcOEt 6:4+0.5% MeOH, **A** and **C**). These compounds have been characterized after TBDMS removal.

*4.10.3. Compounds **14** and **15c***

Chromatography with PE/AcOEt 6:4→0:100 gave **14c** and **15c** both as yellow oils in 66% overall yield. dr: 68:32 [HPLC: column Hypersil ODS 200×2.1 mm, 5 μm, MeOH/H_2O 73:27, flow=0.4 ml/min, t_R 12.45 (**14c**) and 14.05 (**15c**) min; GC–MS: usual method but with final temp=290 °C, t_R 11.79 (**15c**) and 12.16 (**14c**) min. Compound **14c**: R_f 0.26 (PE/AcOEt 1:1, **A** and **C**). $[\alpha]_D^{20}$ +13.2 (*c* 1.68). IR: ν_{max} 3440, 3000, 1711, 1421, 1361, 1224, and 1111. GC–MS (usual method but with final temp=290 °C): t_R 12.16; *m/z* 445 (M^+–108, 0.42), 389 (15), 388 (56), 215 (6.7), 214 (36), 204 (6.3), 203 (44), 199 (7.9), 198 (16), 185 (7.5), 179 (27), 157 (8.1), 156 (48), 106 (11), 100 (7.9), 99 (6.1), 98 (8.8), 92 (7.9), 91 (100), 89 (6.3), 82 (26), 80 (7.3), 77 (5.2), 75 (28), 73 (41), 70 (18), 69 (7.9), 68 (18), 65 (6.9), 59 (12), 57 (5.9), 56 (17), 55 (18), 42 (5.4), 41 (9.2). ^{1}H NMR (300 MHz, DMSO-d_6, rt: four rotamers can be detected with the two highly prevailing in a 59:41 ratio) at 90 °C: 0.04, 0.05, and 0.06 [6H, 3s, Si(CH_3)$_2$]; 0.88 and 0.89 [9H, 2s, SiC(CH_3)$_3$]; 1.86–2.66 [6H, m, CH_2 pyrrolidine, NCOCH_2]; 3.28 [2H, br dd, CH_2NHZ, *J*=12.6, 6.6]; 3.54 [1H, br t, C*H*CH$_2$OSi, *J*=9.3]; 3.51–4.43 [5H, m, C*H*CO, CH_2OSi, NHCH_2Ph]; 5.04 [2H, s, OCH_2Ph]; 6.76 [1H, br s, N*H*Z]; 7.19–7.39 [10H, m, aromatics]; 8.01 (*M*) [1H, br s, N*H*CH$_2$Ph (at rt: br t at 8.26, *J*=6.0)]; 8.30 (*m*) [1H, br s, N*H*CH$_2$Ph (at rt: br t at 8.54, *J*=5.8)]. ^{13}C NMR (75 MHz) (only the signals of the two highly prevailing rotamers have been reported): −5.6 (*m*), −5.5 (*M*), −5.4 (*M*), and −5.3 (*m*) [2C, Si(*C*H$_3$)$_2$]; 17.9 (*M*) and 18.0 (*m*) [*C*(CH$_3$)$_3$]; 25.7 [3C, SiC(*C*H$_3$)$_3$]; 26.0 (*m*), 26.9 (*M*), 27.1 (*M*), and 29.6 (*m*) [2C, *C*H$_2$ pyrrolidine]; 33.6 (*M*) and 33.7 (*m*) [NCO*C*H$_2$]; 36.3 (*m*) and 36.8 (*M*) [*C*H$_2$NHZ]; 41.8 (*M*) and 42.2 (*m*) [NH*C*H$_2$Ph]; 59.2 (*m*) and 59.4 (*M*), 60.1 (*M*) and 60.5 (*m*) [2C, *C*H pyrrolidine]; 62.3 (*m*) and 63.2 (*M*) [*C*H$_2$OSi]; 65.2 [O*C*H$_2$Ph]; 126.6, 126.8, 127.0, 127.7, 128.1 and 128.3 [10C, aromatic *C*H]; 137.1, 139.1 (*m*) and 139.4 (*M*) [2C, aromatic *C*]; 155.9 (*m*) and 156.0 (*M*) [*C*O (Z)]; 169.7 (*m*), 170.1 (*M*), 171.7 (*m*) and 171.8 (*M*) [2C, *C*O]. Compound **15c**: R_f 0.15 (PE/AcOEt 1:1, **A** and **C**). $[\alpha]_D^{20}$ −13.1 (*c* 1.04). IR: ν_{max} 3437, 3005, 1712, 1672, 1497, 1424, 1246, 1191, 1096, and 1002. GC–MS (usual method but with final temp=290 °C): t_R 12.16; *m/z* 445 (M^+–108, 0.36), 390 (7.5), 389 (28), 388 (100), 214 (16), 203 (18), 198 (7.6), 179 (10), 174 (9.7), 156 (19), 91 (58), 82 (8.4), 75 (11), 73 (16), 70 (7.2), 68 (6.0), 56 (5.4), 55 (6.3). ^{1}H NMR (300 MHz, DMSO-d_6, rt: 56:44 mixture of rotamers, remains even at 90 °C) at 90 °C: 0.04, 0.05, and 0.07 [6H, 3s, Si(CH_3)$_2$]; 0.90 [9H, 2s, SiC(CH_3)$_3$]; 1.72–2.70 [6H, m, CH_2 pyrrolidine, NCOCH_2]; 3.21–3.57 (m), 3.62 and 3.74 (AB part of an ABX system, J_{AB}=9.2, J_{AX}=6.1, J_{BX}=2.7), and 4.06–4.40 (m) [8H, CH_2NHZ, C*H*, CH_2OSi, NHCH_2Ph]; 5.04 and 5.04 [2H, AB system, OCH_2Ph, *J*=13.0]; 6.65 (*M*) [1H, br s, N*H*Z]; 6.77 (*m*) [1H, br s, N*H*Z]; 7.22–7.39 [10H, m, aromatics]; 8.02 (*m*) [1H, br s, N*H*CH$_2$Ph (at rt: br t at 8.34, *J*=5.8)]; 8.30 (*M*) [1H, br s, N*H*CH$_2$Ph (at rt: br t at 8.62, *J*=5.7)]. ^{13}C NMR (75 MHz): −5.6 (*m*), −5.53 (*M*), −5.51 (*M*), and −5.4 (*m*) [2C, Si(*C*H$_3$)$_2$]; 17.80 (*M*) and 17.84 (*m*) [*C*(CH$_3$)$_3$]; 25.1 (*M*), 26.8 (*m*), 27.5 (*m*), and 30.0 (*M*) [2C, *C*H$_2$ pyrrolidine]; 25.7 [3C, SiC(*C*H$_3$)$_3$]; 34.0 (*m*) and 34.2 (*M*) [NCO*C*H$_2$]; 36.4 (*M*) and 37.0 (*m*) [*C*H$_2$NHZ]; 41.8 (*m*) and 42.2 (*M*) [NH*C*H$_2$Ph]; 58.9 (*m*) and 59.0 (*M*), 60.3 (*m*) and 60.5 (*M*) [2C, *C*H pyrrolidine]; 61.9 (*M*) and 64.2 (*m*) [*C*H$_2$OSi]; 65.2 [O*C*H$_2$Ph]; 126.5, 126.8, 127.1, 127.68, 127.71, 128.1, and 128.3 [10C, aromatic *C*H]; 137.1, 139.2 (*M*) and 139.5 (*m*) [2C, aromatic *C*]; 155.9 (*M*) and 156.0 (*m*) [*C*O (Z)]; 169.7, 171.8, and 172.0 [2C, *C*O].

*4.10.4. Compounds **14** and **15d***

Chromatography with PE/AcOEt 6:4→45:55 gave **14** and **15d** as an unseparable mixture (yellow foam) in 52% overall yield. dr: 64:36 [HPLC: column Daicel 250×4.6 mm, hexane/^{i}PrOH 85:15, flow=1 ml/min, DAD 220 nm, t_R 4.80 (**14d**) and 7.98 (**15d**) min]. Compounds **14** and **15d**: R_f 0.35 (PE/AcOEt 6:4, **C**). GC–MS: unsuitable for this analysis. Selected ^{1}H NMR data at 120 °C (300 MHz, DMSO-d_6): 0.05, 0.06, 0.07, and 0.08 [6H, 4s, Si(CH_3)$_2$]; 0.90 and 0.91 [9H, 2s, SiC(CH_3)$_3$]; 1.39 and 1.40 [9H, 2s, OC(CH_3)$_3$]; 5.04 and 5.06 [2H, 2s, OCH_2Ph]; 6.25, 6.31, and 6.66 [3H, 3br s, N*H*Z, N*H*Boc]; 7.70, 7.86, and 8.22 [3H, br s, N*H*CH$_2$Ph (at rt: 4br t at 7.97, *J*=5.8; 8.25, *J*=5.8; 8.46, *J*=5.4, and 8.66, *J*=5.7)]. Selected ^{13}C NMR data (75 MHz): −5.5 [2C, Si(*C*H$_3$)$_2$]; 17.76 and 17.84 [*C*(CH$_3$)$_3$]; 25.7 [3C, SiC(*C*H$_3$)$_3$]; 28.0 [3C, OC(*C*H$_3$)$_3$]; 65.3 [*C*H$_2$O]; 78.2, 78.4, 78.6 [O*C*(CH$_3$)$_3$]; 155.1, 155.3, 155.5, 155.6, 155.8, 156.0, 156.1, and 156.2 [*C*O (Z, Boc)]; 169.4, 170.0, 171.3, and 171.9 [2C, *C*O].

*4.10.5. Compounds **14** and **15e***

Chromatography with CH_2Cl_2/AcOEt 8:2+1% ^{i}PrOH→6:4+1% ^{i}PrOH gave **14e** and **15e** both as colorless oils in 66% overall yield. dr: 63:37 (by weight). Compound **14e**: R_f 0.58 (CH_2Cl_2/AcOEt 8:2+1% ^{i}PrOH, **A** and **C**). $[\alpha]_D^{20}$ +12.3 (*c* 1.09). IR: ν_{max} 3428, 2953, 2928, 1738, 1702, 1643, 1439, 1368, 1278, and 1106. GC–MS: unsuitable for this analysis. Selected ^{1}H NMR data (300 MHz, DMSO-d_6, rt: ≈3:1 mixture of rotamers) at 90 °C: 0.03 and 0.04 [6H, 2s, Si(CH_3)$_2$]; 0.88 [9H, s, SiC(CH_3)$_3$]; 1.20 and 1.21 [6H, 2s, C(CH_3)$_2$]; 1.39 [9H, s, OC(CH_3)$_3$]; 3.71 [3H, s, OCH_3]; 5.07 and 5.06 [2H, AB system, OCH_2Ph, *J*=13.2]. ^{13}C NMR (75 MHz): −5.6 and −5.5 [2C, Si(*C*H$_3$)$_2$]; 17.8 [*C*(CH$_3$)$_3$]; 22.7 and 23.9 (*M*), 23.6 and 23.8 (*m*) [2C, C(*C*H$_3$)$_2$]; 24.5 (*M*), 26.4 (*m*), 27.2 (*m*), and 30.6 (*M*) [2C, *C*H$_2$ pyrrolidine]; 25.7 [3C, SiC(*C*H$_3$)$_3$]; 28.0 [3C, OC(*C*H$_3$)$_3$]; 35.0 (*M*) and 36.2 (*m*) [*C*H$_2$CO$_2$Bn]; 48.1 (*m*) and 48.6 (*M*) [*C*HNHBoc]; 51.9 (*m*) and 52.2 (*M*) [*C*(CH$_3$)$_2$]; 54.5 [OCH$_3$]; 58.1 (*m*), 59.3 (*M*), 60.2 (*m*) and 60.3 (*M*) [2C, *C*H pyrrolidine]; 61.8 (*M*), 63.6 (*m*), and 65.4 [2C, *C*H$_2$]; 70.9 (*M*) and 71.0 (*m*) [*C*H$_2$OCO$_2$Me]; 78.0 (*M*) and 78.5 (*m*) [O*C*(CH$_3$)$_3$]; 127.6, 127.8, 127.9, and 128.2 [5C, *C*H of Ph]; 135.88 (*m*) and 135.93 (*M*) [*C* of Ph]; 155.0 [2C, *C*O (carbonate, Boc)]; 169.9 (*m*), 170.1 (*M*), 170.5 (*m*), 170.8 (*M*), 171.1 (*m*), and 171.8 (*M*) [3C, *C*O]. Compound **15e**: R_f 0.33 (CH_2Cl_2/AcOEt

8:2+1% ^{i}PrOH, **A** and **C**). $[\alpha]_D^{20}$ −37.1 (*c* 2.76). IR: ν_{max} 3426, 2952, 2927, 1742, 1660, 1491, 1440, 1368, 1272, 1158, 1092, and 972. GC–MS: unsuitable for this analysis. Selected ^{1}H NMR data (300 MHz, DMSO-d_6, rt: ≈3:1 mixture of rotamers) at 90 °C: 0.06 [6H, s, Si(CH_3)$_2$]; 0.89 [9H, s, SiC(CH_3)$_3$]; 1.25 and 1.26 [6H, 2s, C(CH_3)$_2$]; 1.39 [9H, s, OC(CH_3)$_3$]; 3.71 [3H, s, OCH_3]; 5.10 [2H, s, OCH_2Ph]. ^{13}C NMR (75 MHz): −5.7, −5.6, and −5.4 [2C, Si(*C*H$_3$)$_2$]; 17.9 [*C*(CH$_3$)$_3$]; 23.3 (*m*), 23.4, and 23.6 (*M*) [2C, C(*C*H$_3$)$_2$]; 25.7 [3C, SiC(*C*H$_3$)$_3$]; 26.1 (*M*), 26.7 (*M*), and 28.9 (*m*) [2C, *C*H$_2$ pyrrolidine]; 28.0 [3C, OC(*C*H$_3$)$_3$]; 35.7 (*m*) and 36.2 (*M*) [CH$_2$CO$_2$Bn]; 48.1 (*M*) and 49.4 (*m*) [*C*HNHBoc]; 51.9 (*M*) and 52.4 (*m*) [*C*(CH$_3$)$_2$]; 54.5 (*M*) and 54.8 (*m*) [O*C*H$_3$]; 58.9 (*M*), 59.7 (*m*), 60.3 (*M*), and 61.0 (*m*) [2C, *C*H pyrrolidine]; 62.8 (*M*), 64.0 (*m*), and 65.5 [2C, *C*H$_2$]; 71.0 [*C*H$_2$OCO$_2$Me]; 78.4 (*M*) and 78.5 (*m*) [O*C*(CH$_3$)$_3$]; 127.7, 127.9, 128.3, and 128.6 [5C, *C*H of Ph]; 135.8 [*C* of Ph]; 155.0 [2C, *C*O (carbonate, Boc)]; 169.7 (*M*), 169.9 (*m*), 170.1 (*M*), 170.3 (*m*), 170.5 (*m*), and 170.9 (*M*) [3C, *C*O].

4.10.6. Compounds *14* and *15f*

Chromatography with PE/AcOEt 7:3→2:8 gave **14f** as white foam and **15f** as pale yellow oil in 67% overall yield. dr: 60:40 (by weight). Compound **14f**: R_f 0.41 (PE/AcOEt 6:4, **A** and **C**). $[\alpha]_D^{20}$ +17.8 (*c* 2.16). IR: ν_{max} 3424, 2949, 2928, 1724, 1647, 1436, 1368, 1246, 1156, 1107, 1044, and 834. GC–MS: unsuitable for this analysis. Selected ^{1}H NMR data (300 MHz, DMSO-d_6, rt: 80:20 mixture of rotamers) at 90 °C: −0.02, 0.01, 0.02, and 0.08 [6H, 4s, Si(CH_3)$_2$]; 0.88 [9H, s, SiC(CH_3)$_3$]; 1.25 and 1.30 [6H, 2s, C(CH_3)$_2$]; 1.36 [9H, s, OC(CH_3)$_3$]; 3.72 [3H, s, OCH_3]; 5.02 and 5.06 [2H, AB system, OCH_2Ph, *J*=12.0]. ^{13}C NMR (75 MHz): −5.64 and −5.59 [2C, Si(*C*H$_3$)$_2$]; 17.8 (*M*) and 17.9 (*m*) [*C*(CH$_3$)$_3$]; 22.8 and 24.13 (*M*), 23.6 and 23.8 (*m*) [2C, C(*C*H$_3$)$_2$]; 24.7 (*M*), 26.6 (*m*), 28.9 (*m*), and 30.6 (*M*) [2C, *C*H$_2$ pyrrolidine]; 25.7 [3C, SiC(*C*H$_3$)$_3$]; 27.5 [3C, OC(*C*H$_3$)$_3$]; 36.4 (*M*) and 37.3 (*m*) [*C*H$_2$CO$_2$^{t}Bu]; 48.5 (*m*) and 49.1 (*M*) [*C*HNHZ]; 51.9 (*m*) and 52.3 (*M*) [*C*(CH$_3$)$_2$]; 54.5 [O*C*H$_3$]; 58.3 (*m*), 59.2 (*M*), 60.2 (*m*), and 60.6 (*M*) [2C, *C*H pyrrolidine]; 62.1 (*M*), 64.2 (*m*), 65.2 (*M*) and 65.4 (*m*) [2C, *C*H$_2$]; 70.9 (*M*) and 71.0 (*m*) [*C*H$_2$OCO$_2$Me]; 79.7 (*M*) and 80.1 (*m*) [O*C*(CH$_3$)$_3$]; 127.3, 127.6, 127.7, and 128.2 [5C, *C*H of Ph]; 136.9 [*C* of Ph]; 155.00 (*M*) and 155.05 (*m*), 155.5 (*M*) and 155.7 (*m*) [2C, *C*O (carbonate, Z)]; 168.9 (*m*), 169.1 (*M*), 169.3 (*m*), 170.5 (*M*), 171.1 (*m*), and 171.8 (*M*) [3C, *C*O]. Compound **15f**: R_f 0.30 (PE/AcOEt 6:4, **A** and **C**). $[\alpha]_D^{20}$ −47.1 (*c* 2.03). IR: ν_{max} 3422, 2952, 2927, 1719, 1637, 1438, 1368, 1259, 1151, 1090, and 719. GC–MS: unsuitable for this analysis. Selected ^{1}H NMR data (300 MHz, DMSO-d_6, rt: ≈3:1 mixture of rotamers) at 90 °C: 0.08 [6H, s, Si(CH_3)$_2$]; 0.90 [9H, s, SiC(CH_3)$_3$]; 1.25 and 1.26 [6H, 2s, C(CH_3)$_2$]; 1.40 [9H, s, OC(CH_3)$_3$]; 3.72 [3H, s, OCH_3]; 5.05 and 5.05 [2H, AB system, OCH_2Ph, *J*=13.2]. ^{13}C NMR (75 MHz): −5.6, −5.5, and −5.4 [2C, Si(*C*H$_3$)$_2$]; 17.8 (*m*) and 17.9 (*M*) [*C*(CH$_3$)$_3$]; 23.5 and 23.7 [2C, C(*C*H$_3$)$_2$]; 25.7 [3C, SiC(*C*H$_3$)$_3$]; 26.3 (*M*), 26.6 (*M*), 28.9 (*m*), and 30.1 (*m*) [2C, *C*H$_2$ pyrrolidine]; 27.5 [3C, OC(*C*H$_3$)$_3$]; 37.4 [*C*H$_2$CO$_2$^{t}Bu]; 48.6 (*M*) and 49.6 (*m*) [*C*HNHZ]; 51.9 (*M*) and 52.2 (*m*) [*C*(CH$_3$)$_2$]; 54.5 [O*C*H$_3$]; 58.8 (*M*), 59.7 (*m*), 60.2 (*M*), and 60.7 (*m*) [2C, *C*H pyrrolidine]; 62.9 (*M*), 63.5 (*m*), 65.5 [2C, *C*H$_2$]; 70.9 [*C*H$_2$OCO$_2$Me]; 80.1 (*m*) and 80.2 (*M*) [O*C*(CH$_3$)$_3$]; 127.6, 127.8, 128.16, and 128.24 [5C, *C*H of Ph]; 136.8 [*C* of Ph]; 155.00, 155.4 (*m*) and 155.6 (*M*) [2C, *C*O (carbonate, Z)]; 169.0, 169.2, 169.7, 170.6, and 171.0 [3C, *C*O].

4.10.7. Compounds *14* and *15g*

Chromatography with PE/AcOEt 85:15+1% EtOH→75:25+1% EtOH gave **14** and **15g** as an unseparable mixture (yellow oil) in 47% overall yield. dr: 65:35 [HPLC: column Hypersil Silica 200×4.6 mm, 5 μm, hexane/^{i}PrOH 9:1, flow=1 ml/min, DAD 230, t_R 3.39 (**14g**) and 5.53 (**15g**) min]. Compounds **14** and **15g**: R_f 0.30 (PE/AcOEt 7:3, **A** and **C**). GC–MS: unsuitable for this analysis. Selected ^{1}H NMR data at 90 °C (300 MHz, DMSO-d_6): 0.037, 0.044, 0.087, and 0.094 [12H, 4s, Si(CH_3)$_2$]; 0.87, 0.90, and 0.93 [18H, 3s, SiC(CH_3)$_3$]; 5.01 and 5.03 [2H, 2s, OCH_2Ph]; 6.76 [1H, br s, N*H*Z]; 9.09, 9.15, and 9.29 [1H, 3br s, N*H*Ar (at rt: 4br s at 9.39, 9.41, 9.50, and 9.58]. ^{13}C NMR (75 MHz): −5.4 [4C, Si(*C*H$_3$)$_2$]; 17.8, 17.85, 18.92, 17.95, and 18.0 [2C, *C*(CH$_3$)$_3$]; 25.1, 26.2, 26.8, 26.9, 27.5, 29.8, and 30.2 [2C, *C*H pyrrolidine]; 25.7 [6C, SiC(*C*H$_3$)$_3$]; 33.6, 33.7, 33.9, 34.1, 36.5, 36.7, and 36.9 [2C, (*C*H$_2$)$_2$NHZ]; 58.9, 59.1, 59.3, 59.4, 60.4, 60.5, and 60.8 [2C, *C*H pyrrolidine]; 60.9, 61.0, 61.9, 62.4, 63.3, 64.2, and 65.1 [3C, *C*H$_2$O]; 124.4, 125.1, 125.2, 125.4, 125.5, 125.6, 125.9, 126.0, 126.2, 126.3, 126.7, 126.95, 127.01, 127.7, and 128.3 [9C, aromatic *C*H]; 133.5, 133.9, 134.0, 134.1, 135.1, 135.3, 135.6, 135.9, 137.0, and 137.1 [3C, aromatic *C*]; 155.9 [*C*O (Z)]; 169.7, 170.0, 170.1, 170.3, 170.5, 170.7, and 170.8 [2C, *C*O].

4.10.8. Compounds *14* and *15h*

Chromatography with PE/AcOEt 1:1→3:7 gave **14h** and **15h** both as orange foams in 75% overall yield. dr: 64:36 [HPLC: column Supelco LC18 250×4.6 mm, 5 μm, H$_2$O/MeCN 4:6, flow=1.2 ml/min, DAD 254, t_R 11.91 (**14h**) and 13.21 (**15h**) min]. Compound **14h**: R_f 0.34 (PE/AcOEt 1:1, **A**, **B**, and **C**). $[\alpha]_D^{20}$ +13.9 (*c* 0.96). IR: ν_{max} 3453, 3018, 1709, 1507, 1412, 1213, 1110, and 725. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6, rt: 51:49 mixture of rotamers, remains even at 90 °C) at 90 °C: 0.05, 0.06, and 0.08 [6H, 3s, Si(CH_3)$_2$]; 0.91 [9H, s, SiC(CH_3)$_3$]; 1.83–2.72 [6H, m, CH_2 pyrrolidine, NCOCH_2]; 3.28 [2H, center of m, CH_2NHZ]; 3.56–3.79 [2H, m, CHCH_2OSi]; 3.74 [3H, s, OCH_3]; 4.11 and 4.18 [1H, centers of 2m, C*H*CH$_2$OSi]; 4.43 and 4.49 [1H, 2d, C*H*CONH, *J*=8.7 both]; 5.00 and 5.05 [2H, 2s, OCH_2Ph]; 6.68 and 6.75 [1H, 2br s, N*H*Z, (at rt: 2br t at 7.14 and 7.18, *J*=6.0, 5.7)]; 6.85 and 6.88 [2H, 2d, C*H meta* to OMe, *J*=8.4, 8.1]; 7.27–7.37 [5H, m, aromatics]; 7.46 [2H, d, C*H ortho* to OMe, *J*=8.4]; 9.46 and 9.70 [1H, br s, N*H*-*p*An (at rt: 2s at 9.79 and 10.01)]. ^{13}C NMR (75 MHz): −5.6, −5.52, and −5.46 [2C, Si(*C*H$_3$)$_2$]; 17.78 and 17.83 [*C*(CH$_3$)$_3$]; 25.1, 26.8, 27.5, and 30.1 [2C, *C*H$_2$ pyrrolidine]; 25.7 [3C, SiC(*C*H$_3$)$_3$]; 33.9 and

34.0 [NCOCH_2]; 36.4 and 36.9 [CH_2NHZ]; 55.1 [OCH_3]; 58.9 and 59.1 [$CH$$CH_2$OSi]; 60.5 and 60.8 [$CH$CONH]; 62.1 and 64.4 [$CH_2$OSi]; 65.05 and 65.11 [O$CH_2$Ph]; 113.6 and 113.8 [2C, *C*H *ortho* to OMe]; 120.5 and 121.0 [2C, *C*H *meta* to OMe]; 127.6, 127.7, 128.21, and 128.24 [5C, *C*H of Ph]; 131.7 and 132.3 [*C*-NH]; 137.0 and 137.1 [*C* of Ph]; 155.0, 155.4, 155.8, and 155.9 [2C, *C*-OMe, *C*O (Z)]; 169.6, 169.7, 170.0, and 170.2 [2C, *C*O]. Compound **15h**: R_f 0.23 (PE/AcOEt 1:1, **A**, **B**, and **C**). $[\alpha]_D^{20}$ −60.1 (*c* 1.00). IR: ν_{max} 3440, 2951, 1709, 1598, 1502, 1416, 1192, 1087, and 830. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6, rt: 68:32 mixture of rotamers) at 90 °C: 0.066 and 0.069 [6H, 3s, Si(CH_3)$_2$]; 0.89 [9H, s, SiC(CH_3)$_3$]; 1.89–2.65 [6H, m, CH_2 pyrrolidine, NCOCH_2]; 3.29 [2H, br q, CH_2NHZ, *J*=6.5]; 3.56–3.90 [2H, m, CHCH_2OSi]; 3.75 [3H, s, OCH_3]; 4.09 [1H, br s, CHCH_2OSi]; 4.48 [1H, t, CHCONH, *J*=7.5]; 5.03 [2H, s, OCH_2Ph]; 6.77 [1H, br s, NHZ (at rt: 2br t at 7.16 (*m*) and 7.22 (*M*), *J*=5.7 both)]; 6.87 [2H, dt, CH *meta* to OMe, *J*=9.0, 2.8]; 7.28–7.38 [5H, m, aromatics]; 7.45 [2H, dt, CH *ortho* to OMe, *J*=9.0, 2.7]; 9.50 [1H, br s, NH-*p*An (at rt: 2s at 9.84 (*M*) and 9.94 (*m*)]. ^{13}C NMR (75 MHz): −5.6, −5.4, and −5.3 [2C, Si(CH_3)$_2$]; 17.8 (*M*) and 17.9 (*m*) [C(CH_3)$_3$]; 25.7 [3C, SiC(CH_3)$_3$]; 25.9, 26.9, and 29.8 [2C, CH_2 pyrrolidine]; 33.4 [NCOCH_2]; 36.3 (*m*) and 36.7 (*M*) [CH_2NHZ]; 55.0 [OCH_3]; 59.2 (*m*) and 59.4 (*M*) [$CH$$CH_2$OSi]; 60.6 [$CH$CONH]; 62.1 (*m*) and 63.3 (*M*) [CH_2OSi]; 65.1 [OCH_2Ph]; 113.66 (*M*) and 113.74 (*m*) [2C, CH *ortho* to OMe]; 120.4 (*M*) and 121.3 (*m*) [2C, CH *meta* to OMe]; 127.6, 127.7, 128.21, and 128.24 [5C, CH of Ph]; 131.5 (*m*) and 132.2 (*M*) [*C*-NH]; 137.0 (*m*) and 137.1 (*M*) [*C* of Ph]; 155.0 (*M*), 155.5 (*m*), and 155.9 [2C, *C*-OMe, *C*O (Z)]; 169.5, 169.7, and 170.0 [2C, *C*O].

4.10.9. Compounds *14* and *15i*

Chromatography with CH_2Cl_2/AcOEt 9:1+2% MeOH→8:2+2% MeOH gave **14i** and **15i** both as colorless oils in 81% overall yield. dr: 68:32 (by ^{1}H NMR). Compound **14i**: R_f 0.33 (CH_2Cl_2/AcOEt 9:1+2% MeOH, **A** and **B**). $[\alpha]_D^{20}$ +100.2 (*c* 1.80). Compound **15i**: R_f 0.44 (CH_2Cl_2/AcOEt 9:1+2% MeOH, **A** and **B**). $[\alpha]_D^{20}$ −31.1 (*c* 2.04). The following spectroscopic data have been taken on the purified diastereomeric mixture. GC–MS: a partial decomposition occurred. Selected ^{1}H NMR data (300 MHz, DMSO-d_6, rt: two diastereoisomer both as a ≈1:1 mixture of rotamers): −0.23 and −0.20 (minor diast.), 0.07 and 0.08 (major diast.) [6H, 4s, Si(CH_3)$_2$]; 0.72, 0.90, 0.91, 1.10, 1.24, and 1.25 [15H, 6s, SiC(CH_3)$_3$, C(CH_3)$_2$]; 3.67, 3.68, and 3.69 [3H, 3s, OCH_3]. ^{13}C NMR (75 MHz): −6.1, −5.8, and −5.5 [2C, Si(CH_3)$_2$]; 17.6 and 17.8 [C(CH_3)$_3$]; 22.7 and 22.9, 23.53, and 23.55 [2C, C(CH_3)$_2$]; 24.9, 25.1, 26.6, 28.8, 27.5, and 30.7 [2C, CH_2 pyrrolidine]; 25.6 and 25.8 [3C, SiC(CH_3)$_3$]; 51.6, 51.9, and 52.0 [C(CH_3)$_2$]; 54.5 and 54.9 [OCH_3]; 59.2, 59.6, 59.8, and 60.2 [2C, CH pyrrolidine]; 62.2, 62.6, 63.1, and 63.3 [2C, CH_2]; 70.8, 71.1, and 71.9 [CH_2OCO$_2$Me]; 126.3, 126.6, 127.7, 128.0, 128.2, 128.9, and 129.3 [5C, CH of Ph]; 137.0, 137.4, and 137.6 [5C, CH of Ph]; 154.9 and 155.0 [CO (carbonate)]; 168.8, 170.0, and 171.3 [2C, CO].

4.11. General procedure for TBDMS removal on compounds *14* and *15*

A solution of the substrate, either **14** or **15** or a mixture of both (for preparative purposes), in MeCN was cooled to 0 °C and treated with 40% HF (1:20 ratio HF/MeCN) was reached. After stirring at 0 °C for 2–4 h, the reaction was quenched with 5% $NaHCO_3$ saturated with NaCl and extracted with AcOEt. After drying, the solvent was evaporated and the crude directly chromatographed with the appropriate PE/AcOEt mixture.

4.11.1. Compounds *16* and *17*

Chromatography with CH_2Cl_2/AcOEt 4:6+1% MeOH→2:8+2% MeOH gave **16** and **17** both as white foams in 94% overall yield. Compound **16**: R_f 0.21 (CH_2Cl_2/AcOEt 4:6+1% MeOH, **A** and **C**). Anal. Found: C, 64.70; H, 6.80; N, 7.90. $C_{29}H_{37}N_3O_7$ requires C, 64.55; H, 6.91; N, 7.79. $[\alpha]_D^{20}$ +6.9 (*c* 2.08) and +28.8 (*c* 2.08, EtOH). IR: ν_{max} 3423, 3004, 1690, 1643, 1491, 1434, 1245, 1155, and 1041. GC–MS: unsuitable for this analysis. ^{1}H NMR (200 MHz, DMSO-d_6, rt: 66:34 mixture of rotamers) at 100 °C: 1.38 [9H, s, OC(CH_3)$_3$]; 1.62–4.78 [13H, m, CH_2 pyrrolidine, CH_2CO$_2$Bn, CH_2Ph, CH_2OH, 3CH]; 5.10 [2H, s, OCH_2Ph]; 6.77 [1H, br s, NHBoc]; 7.21–7.36 [10H, m, aromatics]; 7.74 [1H, br s, NHCH_2Ph (at rt: br s at 7.99 (*m*))]; 8.34 [1H, br s, NHCH_2Ph (at rt: br s at 8.69 (*M*))]. ^{13}C NMR (50 MHz): 24.5 (*M*), 26.6 (*m*), 27.2 (*m*), and 29.7 (*M*) [2C, CH_2 pyrrolidine]; 28.0 [3C, OC(CH_3)$_3$]; 35.0 (*M*) and 35.9 (*m*) [CH_2CO$_2$Bn]; 41.7 (*m*) and 42.2 (*M*) [NHCH_2Ph]; 48.5 (*m*) and 48.9 (*M*) [CHNHBoc]; 58.8 (*m*) and 59.8 (*M*), 60.0 (*M*) and 60.4 (*m*) [2C, CH pyrrolidine]; 62.4 and 65.3 [2C, CH_2O]; 78.2 (*M*) and 78.6 (*m*) [OC(CH$_3$)$_3$]; 126.5, 126.7, 127.1, 127.56, 127.64, 127.8, 128.1, and 128.3 [10C, aromatic CH]; 136.0 (*m*) and 136.1 (*M*), 139.0 (*m*) and 139.4 (*M*) [2C, aromatic *C*]; 155.1 (*M*) and 155.4 (*m*) [CO (Boc)]; 169.6, 170.0, 170.1, 170.3, 171.4, and 171.8 [3C, CO]. Compound **17**: R_f 0.36 (CH_2Cl_2/AcOEt 4:6+1% MeOH, **A** and **C**). Anal. Found: C, 64.45; H, 6.85; N, 7.95. $C_{29}H_{37}N_3O_7$ requires C, 64.55; H, 6.91; N, 7.79. $[\alpha]_D^{20}$ −60.7 (*c* 1.98) and −46.3 (*c* 2.06, EtOH). IR: ν_{max} 3427, 2998, 1710, 1658, 1491, 1429, 1296, 1157, and 1053. GC–MS: unsuitable for this analysis. ^{1}H NMR (200 MHz, DMSO-d_6, rt: 77:23 mixture of rotamers) at 100 °C: 1.39 [9H, s, OC(CH_3)$_3$]; 1.90–2.20 [4H, m, CH_2 pyrrolidine]; 2.66 and 2.82 [2H, AB part of an ABX system, CH_2CO$_2$Bn, J_{AB}=16.2, J_{AX}=7.7, J_{BX}=6.1]; 3.45–4.80 [7H, m, CH_2Ph, CH_2OH, 3CH]; 5.07 [2H, s, OCH_2Ph]; 6.79 [1H, br s, NHBoc]; 7.21–7.35 [10H, m, aromatics]; 8.05 [1H, br s, NHCH_2Ph (at rt: 2br s at 8.25 (*M*) and 8.55 (*m*))]. ^{13}C NMR (50 MHz): 25.4 (*m*), 27.3 (*M*), 27.5 (*M*), and 29.9 (*m*) [2C, CH_2 pyrrolidine]; 28.0 [3C, OC(CH_3)$_3$]; 36.1 (*M*) and 36.5 (*m*) [CH_2CO$_2$Bn]; 41.8 (*M*) and 42.5 (*m*) [NHCH_2Ph]; 48.2 (*M*) and 49.3 (*m*) [CHNHBoc]; 59.3, 60.5, and 61.2 [2C, CH pyrrolidine]; 60.8 (*m*) and 62.5 (*M*), 65.4 [2C, CH_2O]; 78.3 [OC(CH$_3$)$_3$]; 126.5, 126.7, 127.0, 127.6, 127.8, 128.1, 128.2, and 128.3 [10C, aromatic CH]; 135.9, 138.8 (*m*), and 139.2 (*M*) [2C, aromatic

C]; 154.6 (*m*) and 155.0 (*M*) [*C*O (Boc)]; 169.6, 170.1, 170.3, 170.5, 171.5, and 172.1 [3C, *C*O].

4.11.2. Compounds **18** and **19**

Chromatography with CH_2Cl_2/AcOEt 4:6+1% MeOH→AcOEt+1% MeOH gave **18** and **19** both as white foams in 92% overall yield. Compound **18**: R_f 0.30 (CH_2Cl_2/AcOEt 4:6+1% MeOH, **A** and **C**). Anal. Found: C, 64.60; H, 6.95; N, 7.70. $C_{29}H_{37}N_3O_7$ requires C, 64.55; H, 6.91; N, 7.79. $[\alpha]_D^{20}$ +32.3 (*c* 3.15) and +34.9 (*c* 1.62, EtOH). IR: ν_{max} 3423, 3386, 3017, 1712, 1648, 1423, 1195, and 1046. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6, rt: 91:9 mixture of rotamers): 1.37 [9H, s, OC(CH_3)$_3$]; 1.58–2.89 (m), 2.59 and 2.85 (*M*) (AB part of an ABX system, J_{AB}=17.0, J_{AX}=10.7, J_{BX}=2.5) [6H, CH_2 pyrrolidine, CH_2CO$_2$Bn]; 3.82–4.72 (m), 4.21 and 4.29 (*M*) (AB part of an ABX system, J_{AB}=15.6, J_{AX}=J_{BX}=7.7), 4.97 (br t, *J*=5.1) [7H, m, CH_2Ph, CH_2OH, 3C*H*]; 5.10 and 5.10 [2H, AB system, OCH_2Ph, *J*=13.4]; 7.20–7.38 [11H, m, aromatics, *NH*Boc]; 8.24 (*M*) [1H, br t, N*H*CH$_2$Ph, *J*=6.0]; 8.45 (*m*) [1H, br t, N*H*CH$_2$Ph, *J*=5.9]. ^{13}C NMR (75 MHz): 24.4 (*m*), 26.2 (*M*), 26.7 (*M*), and 28.9 (*m*) [2C, *C*H$_2$ pyrrolidine]; 28.1 [3C, OC(*C*H$_3$)$_3$]; 35.8 (*M*) and 37.6 (*m*) [*C*H$_2$CO$_2$Bn]; 41.8 (*M*) and 42.4 (*m*) [NH*C*H$_2$Ph]; 49.0 (*M*) and 49.1 (*m*) [*C*HNHBoc]; 59.0 (*M*), 59.7 (*m*), 59.9 (*M*), and 60.3 (*m*) [2C, *C*H pyrrolidine]; 61.8 and 65.7 [2C, *C*H$_2$O]; 78.0 [O*C*(CH$_3$)$_3$]; 126.5, 126.6, 126.8, 127.0, 127.1, 127.7, 127.8, 127.9, 128.1, 128.2, and 128.3 [10C, aromatic *C*H]; 135.9, 139.2 (*m*), and 139.4 (*M*) [2C, aromatic *C*]; 154.2 (*m*) and 155.1 (*M*) [*C*O (Boc)]; 169.6 (*m*), 169.7 (*m*), 170.0 (*M*), 170.2 (*M*), 171.1 (*m*), and 171.5 (*M*) [3C, *C*O]. Compound **19**: R_f 0.44 (CH_2Cl_2/AcOEt 4:6+1% MeOH, **A** and **C**). Anal. Found: C, 64.40; H, 7.00; N, 7.80. $C_{29}H_{37}N_3O_7$ requires C, 64.55; H, 6.91; N, 7.79. $[\alpha]_D^{20}$ −1.5 (*c* 1.67) and −3.4 (*c* 1.30, EtOH). IR: ν_{max} 3428, 2975, 1703, 1658, 1494, 1426, 1369, 1190, and 1080. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6, rt: two major rotamers in a 49:51 ratio) at 100 °C: 1.38 [9H, s, OC(CH_3)$_3$]; 1.80–3.00 [6H, m, CH_2 pyrrolidine, CH_2CO$_2$Bn]; 3.50–4.90 (m), 4.10 (quintuplet, *J*=5.4) [7H, CH_2Ph, CH_2OH, 3C*H*]; 5.09 [2H, s, OCH_2Ph]; 6.78 [1H, br s, N*H*Boc]; 7.19–7.40 [10H, m, aromatics]; 8.02 [1H, br s, N*H*CH$_2$Ph (at rt: br t at 8.26, *J*=6.0)]; 8.52 [1H, br s, N*H*CH$_2$Ph (at rt: br t at 8.83, *J*=5.6)]. ^{13}C NMR (75 MHz): 25.5, 27.1, 28.9, and 30.1 [2C, *C*H$_2$ pyrrolidine]; 28.02 and 28.06 [3C, OC(*C*H$_3$)$_3$]; 35.4 and 36.5 [*C*H$_2$CO$_2$Bn]; 41.8 and 42.2 [NH*C*H$_2$Ph]; 48.5 and 48.7 [*C*HNHBoc]; 59.7, 59.8, 60.4, and 60.6 [2C, *C*H pyrrolidine]; 60.2 and 61.9, 65.4 and 65.6 [2C, *C*H$_2$O]; 78.2 and 78.4 [O*C*(CH$_3$)$_3$]; 126.6, 126.7, 127.0, 127.6, 127.7, 127.8, 127.9, 128.1, 128.2, and 128.3 [10C, aromatic *C*H]; 135.9 and 136.0, 138.7 and 139.1 [2C, aromatic *C*]; 154.9 and 155.2 [*C*O (Boc)]; 169.7, 169.9, 170.8, and 172.1 [3C, *C*O].

4.11.3. Compounds **30** and **31**

Chromatography with PE/Me$_2$CO 1:1+1% EtOH→Me$_2$CO+2% EtOH gave **30** as a white solid and **31** as a yellow oil in 89% overall yield. Compound **30**: R_f 0.18 (PE/Me$_2$CO 1:1+1% EtOH, **A** and **C**). Anal. Found: C, 65.70; H, 6.75; N, 9.35. $C_{24}H_{29}N_3O_5$ requires C, 65.59; H, 6.65; N, 9.56. $[\alpha]_D^{20}$ +18.4 (*c* 1.00, EtOH). Mp: 147.5–148.1 °C (PE/Me$_2$CO). IR (KBr): ν_{max} 3430, 3325, 3293, 2950, 2885, 1680, 1652, 1633, 1550, 1441, 1283, 1262, and 700. GC–MS (usual method but with final temp=290 °C): decomposes in the column. ^{1}H NMR (300 MHz, DMSO-d_6, rt: 53:47 mixture of rotamers, remains even at 90 °C): 1.66–2.67 [6H, m, CH_2 pyrrolidine, NCOCH_2]; 3.16–4.37 [6H, m, CH_2NHZ, NHCH_2Ph, CH_2OH]; 4.00 and 4.07 [1H, centers of 2m, C*H*CH$_2$OH]; 4.68 and 4.96 [1H, 2br t, C*H*CO, *J*=5.7, 5.6]; 5.01 [2H, s, OCH_2Ph]; 7.13–7.40 [11H, m, aromatics, N*H*Z (at 90 °C: 2br s at 6.66 and 6.74)]; 8.29 and 8.59 [1H, 2br t, N*H*CH$_2$Ph, *J*=5.8 both (at 90 °C: 2br s at 7.98 and 8.28)]. ^{13}C NMR (75 MHz): 25.1, 26.6, 27.4, and 29.9 [2C, *C*H$_2$ pyrrolidine]; 33.9 and 34.2 [NCO*C*H$_2$]; 36.5 and 37.1 [*C*H$_2$NHZ]; 41.8 and 42.2 [NH*C*H$_2$Ph]; 59.4, 59.6, 60.2, and 60.5 [2C, *C*H pyrrolidine]; 60.6 and 62.5 [*C*H$_2$OH]; 65.2 [O*C*H$_2$Ph]; 126.6, 126.8, 127.1, 127.7, 128.2, and 128.3 [10C, aromatic *C*H]; 137.1, 139.3, and 139.6 [2C, aromatic *C*]; 155.95 and 156.00 [*C*O (Z)]; 169.7, 169.8, 171.9, and 172.1 [2C, *C*O]. Compound **31**: R_f 0.37 (PE/Me$_2$CO 1:1+1% EtOH, **A** and **C**). Anal. Found: C, 65.50; H, 6.70; N, 9.45. $C_{24}H_{29}N_3O_5$ requires C, 65.59; H, 6.65; N, 9.56. $[\alpha]_D^{20}$ −7.6 (*c* 1.00, EtOH). IR: ν_{max} 3433, 2950, 1707, 1641, 1501, 1413, 1247, and 1071. GC–MS (usual method but with final temp=290 °C): decomposes in the column. ^{1}H NMR (300 MHz, DMSO-d_6, rt: 56:44 mixture of rotamers, remains even at 90 °C): 1.80–2.68 [6H, m, CH_2 pyrrolidine, NCOCH_2]; 3.20–5.00 [10H, m, CH_2NHZ (at 90 °C: br q at 3.28, *J*=6.3), NHCH_2Ph, CH_2OH, C*H*, OCH_2Ph]; 7.20–7.36 [11H, m, aromatics, N*H*Z (at 90 °C: br s at 6.74)]; 8.40 and 8.70 [1H, 2br s, N*H*CH$_2$Ph (at 90 °C: 2br s at 8.11 and 8.47)]. ^{13}C NMR (75 MHz): 25.8, 27.5, 27.7, and 29.9 [2C, *C*H$_2$ pyrrolidine]; 33.6 and 34.1 [NCO*C*H$_2$]; 36.4 and 36.8 [*C*H$_2$NHZ]; 41.9 and 42.2 [NH*C*H$_2$Ph]; 59.7, 59.9, 60.3, and 61.1 [2C, *C*H pyrrolidine]; 60.6 and 62.6 [*C*H$_2$OH]; 65.2 [O*C*H$_2$Ph]; 126.6, 126.8, 127.0, 127.8, 128.2, and 128.4 [10C, aromatic *C*H]; 137.1, 139.0, and 139.3 [2C, aromatic *C*]; 155.99 and 156.04 [*C*O (Z)]; 170.0, 170.3, 172.5, and 172.7 [2C, *C*O].

4.11.4. Compounds **36** and **37**

Chromatography with PE/Me$_2$CO 1:1→3:7 gave **36** and **37** both as white foam in 98% overall yield. Compound **36**: R_f 0.18 (PE/Me$_2$CO 1:1, **A** and **C**). Anal. Found: C, 62.75; H, 6.85; N, 10.15. $C_{29}H_{38}N_4O_7$ requires C, 62.80; H, 6.91; N, 10.10. $[\alpha]_D^{20}$ +1.8 (*c* 0.94). IR: ν_{max} 3429, 2998, 1693, 1499, 1418, 1230, 1155, and 1087. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6, rt: four rotamers can be detected with the two highly prevailing (≈90%) in a 53:47 ratio) at 120 °C (two rotamers): 1.39 [9H, s C(CH_3)$_3$]; 1.64–4.75 [13H, m, CH_2 pyrrolidine, NHCH_2Ph, CH_2OH, CH_2NHZ, C*H*]; 5.06 [2H, s, OCH_2Ph]; 6.31 and 6.57 [2H, 2br s, N*H*Z, *NH*Boc (at rt: br s at 6.81 (*NH*Boc, one rotamer), 2d at 6.90 and 6.99 (N*H*Z), *J*=7.5, 6.3)]; 7.19–7.37 [10H, m, aromatics]; 7.62 and 8.18 [1H, 2br s, N*H*CH$_2$Ph (at rt: 2br t at 7.88 and 8.62, *J*=5.8, 5.4)]. ^{13}C NMR (75 MHz) (only the signals of the two

highly prevailing rotamers have been reported): 24.5, 26.7, 27.3, and 29.8 [2C, CH_2 pyrrolidine]; 27.9 and 28.0 [3C, $OC(CH_3)_3$]; 40.8, 41.7, 41.9, and 42.5 [2C, CH_2N]; 51.4 [*C*HNHBoc]; 59.0, 59.7, 60.1, and 60.8 [2C, *C*H pyrrolidine]; 62.6, 65.3, and 65.4 [2C, CH_2O]; 78.4 and 78.7 [$OC(CH_3)_3$]; 126.5, 126.7, 127.2, 127.6, 127.7, 128.1, 128.21, 128.24, and 128.3 [10C, aromatic *C*H]; 136.9, 137.0, 139.2, and 139.3 [2C, aromatic *C*]; 155.3, 155.7, 156.0, and 156.2 [2C, *C*O (Z and Boc)]; 169.6, 169.9, 171.3, and 171.8 [2C, *C*O]. Compound **37**: R_f 0.39 (PE/Me_2CO 1:1, **A** and **C**). Anal. Found: C, 62.95; H, 6.80; N, 10.25. $C_{29}H_{38}N_4O_7$ requires C, 62.80; H, 6.91; N, 10.10. $[\alpha]_D^{20}$ −21.1 (*c* 1.00, EtOH). IR: ν_{max} 3437, 3026, 1703, 1644, 1491, 1252, 1155, and 1038. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6, rt: four rotamers can be detected with the two highly prevailing (≈80%) in a ≈2:1 ratio) at 120 °C: 1.40 [9H, s C(CH_3)$_3$]; 1.85–2.18 [4H, CH_2 pyrrolidine]; 3.23–3.42 (m), 3.57 and 3.65 (AB part of an ABX system, J_{AB}=11.1, J_{AX}=4.7, J_{BX}=6.1), 4.25–5.06 [9H, NHCH_2Ph, CH_2OH, CH_2NHZ, C*H*]; 5.05 [2H, s, OCH_2Ph]; 6.24 and 6.64 [2H, 2br s, N*H*Z, *NH*Boc]; 7.19–7.37 [10H, m, aromatics]; 8.02 [1H, br s, N*H*CH_2Ph (at rt: 2br t at 8.36 and 8.58, *J*=5.7, 5.8)]. ^{13}C NMR (75 MHz) (this spectrum is very complex, due to the presence of four rotamers; only the highly prevailing signals have been reported): 26.0, 27.3, 27.6, and 28.3 [2C, CH_2 pyrrolidine]; 28.0 [3C, $OC(CH_3)_3$]; 41.8 [2C, CH_2N]; 51.3 [*C*HNHBoc]; 59.4, 60.4, and 61.4 [2C, *C*H pyrrolidine]; 62.4 and 65.3 [2C, CH_2O]; 78.3 and 78.5 [$OC(CH_3)_3$]; 126.6, 126.7, 126.9, 127.1, 127.5, 127.6, 127.7, 128.1, 128.2, and 128.3 [10C, aromatic *C*H]; 136.9, 138.8, and 139.2 [2C, aromatic *C*]; 155.3, and 156.2 [2C, *C*O (Z and Boc)]; 170.2 and 172.1 [2C, *C*O].

4.11.5. Compounds *50* and *51*

Chromatography with PE/Me_2CO 4:6→4:6+2% EtOH gave **50** and **51** both as white foams in 77% overall yield (unoptimized). Both have been only partially characterized only in order to identify them. Compound **50**: R_f 0.22 (PE/Me_2CO 4:6, **A** and **C**). Selected ^{1}H NMR data at 90 °C (300 MHz, DMSO-d_6, 61:39 mixture of rotamers even at 90 °C): 4.54 [2H, s, ArCH_2OH]; 5.01 and 5.04 [2H, 2s, OCH_2Ph]; 6.74 [1H, br s, N*H*Z]; 7.10 and 7.13 [1H, 2 t, C*H* *para* to NH, *J*=7.1, 6.6]; 7.17–7.38 [7H, m, aromatics]; 7.60 and 7.63 [1H, 2d, C*H* *ortho* to NH, *J*=8.7, 8.1]; 9.25 (*M*) and 9.43 (*m*) [1H, 2s, N*H*Ar (at rt: 2s at 9.45 and 9.63]. ^{13}C NMR (75 MHz): 25.0 (*m*), 26.7 (*M*), 27.2 (*M*), and 30.0 (*m*) [2C, *C*H pyrrolidine]; 33.8 (*M*) and 34.2 (*m*) [NCO*C*H_2]; 36.5 (*m*) and 36.8 (*M*) [*C*H_2NHZ]; 59.4 (*M*) and 59.6 (*m*), 60.8 (*M*) and 61.0 (*m*) [2C, *C*H pyrrolidine]; 60.2, 60.4, 60.6, 62.3, and 65.2 [3C, *C*H_2O]; 123.3, 124.3, 124.5, 125.1, 127.0, 127.2, 127.7, and 128.3 [9C, aromatic *C*H]; 134.2 (*M*) and 134.9 (*m*), 135.0 (*m*) and 135.6 (*M*), and 137.1 [3C, aromatic *C*]; 156.0 [*C*O (Z)]; 169.9, 170.6, and 170.8 [2C, *C*O]. Compound **51**: R_f 0.32 (PE/Me_2CO 4:6, **A** and **C**). ^{1}H NMR (300 MHz, DMSO-d_6, rt: 67:33 mixture of rotamers) at 90 °C: 1.93–2.30 [4H, m, CH_2 pyrrolidine]; 2.61 [2H, center of m, CH_2CO]; 3.32 [2H, q, CH_2NH, *J*=6.6]; 3.60 [2H, br s, CH_2OH]; 4.10 [1H, quintuplet, C*H*CH_2OH, *J*=5.4]; 4.47–4.58 [2H, m, ArCH_2OH]; 4.77 [1H, center of m, C*H*CONH]; 5.04 [2H, s, OCH_2Ph]; 6.79 [1H, br s, N*H*Z]; 7.13 [1H, t, C*H* *para* to NH, *J*=7.4]; 7.23 [1H, dt, C*H* *para* to CH_2OH, *J*=7.6, 1.8]; 7.28–7.39 [6H, m, aromatics]; 7.64 [1H, d, C*H* *ortho* to NH, *J*=7.8]; 9.35 [1H, br s, N*H*Ar (at rt: 2s at 9.43 and 9.80)]. ^{13}C NMR (75 MHz): 26.0, 27.4, and 29.9 [2C, *C*H pyrrolidine]; 33.6 (*M*) and 34.0 (*m*) [NCO*C*H_2]; 36.4 (*m*) and 36.7 (*M*) [*C*H_2NHZ]; 59.9 (*M*) and 60.0 (*m*), 61.3 (*M*) and 61.8 (*m*) [2C, *C*H pyrrolidine]; 59.9, 60.6, 61.8, 62.2, and 65.2 [3C, *C*H_2O]; 122.9, 124.3, 125.2, 127.0, 127.2, 127.4, 127.7, and 128.3 [9C, aromatic *C*H]; 133.7 (*M*) and 134.6 (*m*), 135.2 (*m*) and 135.6 (*M*), and 137.1 [3C, aromatic *C*]; 156.0 [*C*O (Z)]; 170.7, 170.8, and 171.1 [2C, *C*O].

4.12. General procedure for eight-membered lactone formation

(a) Benzyl ether removal: to a solution of **16**, **17**, **18**, or **19** (193 mg, 357.7 μmol) in EtOH (5 ml) Pd/C (19 mg) was added and the mixture was hydrogenated for 1 h. The catalyst was filtered and the solvent was removed. The crude hydroxy acid was dissolved in dry CH_2Cl_2 and dry toluene was added trice and evaporated to furnish a white solid. (b) Cyclization: a solution of the previously obtained hydroxy acid in dry CH_2Cl_2 (179 ml, 2 mM) was cooled to 0 °C and treated with Et_3N (150 μl, 1.07 mmol) and PyBOP (279 mg, 536.6 μmol). After 10 min the solution was refluxed for 40–45 h (acid from **16** and **18**) or 19–29 h (acid from **17** and **19**). This solution was washed with 5% $NaHCO_3$, dried, and concentrated under reduce pressure.

4.12.1. (5S,8R,10aR)-N-Benzyl-5-[(tert-butoxycarbonyl)-amino]-octahydro-3,6-dioxo-1H-pyrrolo[2,1-c][1,4]-oxazocine-8-carboxamide *20*

Chromatography with CH_2Cl_2/AcOEt 4:6 gave **20** as a pale yellow solid in 86% yield. R_f 0.38 (CH_2Cl_2/AcOEt 4:6, **A**, **C**, and **D**). Anal. Found: C, 61.35; H, 6.80; N, 9.65. $C_{22}H_{29}N_3O_6$ requires C, 61.24; H, 6.77; N, 9.74. $[\alpha]_D^{20}$ −8.8 (*c* 1.92, EtOH). Mp: 127.3–129.0 °C (CH_2Cl_2/AcOEt). IR: ν_{max} 3430, 3002, 1758, 1694, 1641, 1158, 1130, and 828. GC–MS: unsuitable for this analysis. ^{1}H NMR (200 MHz, DMSO-d_6, rt: 82:18 mixture of rotamers): 1.37 [9H, s, $OC(CH_3)_3$]; 1.69–2.22 [4H, m, CH_2 pyrrolidine]; 2.42 and 3.24 (*M*) [2H, AB part of an ABX system, CH_2CO, J_{AB}=13.2, J_{AX}=11.0, J_{BX}=6.6]; 4.17–4.48 [6H, m, CH_2Ph, CH_2O, C*H* pyrrolidine]; 4.90 (*M*) [1H, dt, C*H*NHBoc, *J*=10.6, 7.4]; 6.77 (*m*) [1H, d, N*H*Boc, *J*=7.2]; 6.94 (*M*) [1H, d, N*H*Boc, *J*=7.8]; 7.18–7.34 [5H, m, aromatics]; 8.25 (*M*) [1H, br t, N*H*CH_2Ph, *J*=5.9]; 8.41 (*m*) [1H, br t, N*H*CH_2Ph, *J*=5.7]. ^{13}C NMR (50 MHz): 26.9 and 27.5 [2C, CH_2 pyrrolidine]; 28.1 [3C, $OC(CH_3)_3$]; 41.2 and 41.8 [2C, NHCH_2Ph, CH_2CO]; 50.3 (*M*) and 51.3 [*C*HNHBoc]; 59.8, 60.7 (*m*), and 61.1 (*M*) [2C, *C*H pyrrolidine]; 71.8 (*M*) and 72.3 (*m*) [CH_2O]; 78.7 [$OC(CH_3)_3$]; 126.6 [*C*H *para* (Ph)]; 126.8 [2C, *C*H *ortho* (Ph)]; 128.2 [2C, *C*H *meta* (Ph)]; 139.3 [*C* (Ph)]; 154.0 (*m*) and 154.6 (*M*) [*C*O (Boc)]; 170.3, 171.1, and 173.2 [3C, *C*O].

4.12.2. Stereoisomer (5S,8S,10aR) ***21***

Chromatography with CH_2Cl_2/AcOEt 4:6 gave **21** as a white foam in 90% yield. R_f 0.34 (CH_2Cl_2/AcOEt 4:6, **A**, **C**, and **D**). Anal. Found: C, 61.45; H, 6.65; N, 9.55. $C_{22}H_{29}N_3O_6$ requires C, 61.24; H, 6.77; N, 9.74. $[\alpha]_D^{20}$ −62.6 (*c* 0.90, EtOH). IR: ν_{max} 3417, 2959, 1745, 1704, 1666, 1255, 1157, and 1011. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6, rt: 86:14 mixture of rotamers): 1.34 (*m*) and 1.38 (*M*) [9H, s, OC(CH_3)$_3$]; 1.76–2.18 [4H, m, CH_2 pyrrolidine]; 2.60 and 3.05 (*M*) [2H, AB part of an ABX system, CH_2CO, J_{AB}=14.3, J_{AX}=10.8, J_{BX}=5.5]; 4.21–4.79 [7H, m, CH_2Ph, CH_2O, C*H* pyrrolidine, C*H*NHBoc]; 6.89 (*m*) [1H, d, N*H*Boc, *J*=6.6]; 7.18 (*M*) [1H, d, N*H*Boc, *J*=7.8]; 7.21–7.35 [5H, m, aromatics]; 8.04 [1H, br t, N*H*CH$_2$Ph, *J*=6.0]. ^{13}C NMR (75 MHz): 27.6 [2C, *C*H$_2$ pyrrolidine]; 28.1 [3C, OC(*C*H$_3$)$_3$]; 39.7 and 41.9 [2C, NH*C*H$_2$Ph, *C*H$_2$CO]; 49.2 (*m*) and 49.3 (*M*) [*C*HNHBoc]; 60.2 and 61.5 [2C, *C*H pyrrolidine]; 72.2 (*M*) and 72.8 (*m*) [*C*H$_2$O]; 78.3 [O*C*(CH$_3$)$_3$]; 126.6 [*C*H *para* (Ph)]; 126.9 [2C, *C*H *ortho* (Ph)]; 128.2 [2C, *C*H *meta* (Ph)]; 139.1 [*C* (Ph)]; 154.8 [*C*O (Boc)]; 170.6, 170.7, and 172.9 [3C, *C*O].

4.12.3. Stereoisomer (5R,8S,10aR) ***23***

Chromatography with CH_2Cl_2/AcOEt 4:6 gave **23** as a white foam in 81% yield. R_f 0.41 (CH_2Cl_2/AcOEt 4:6, **A**, **C**, and **D**). Anal. Found: C, 61.30; H, 6.70; N, 9.80. $C_{22}H_{29}N_3O_6$ requires C, 61.24; H, 6.77; N, 9.74. $[\alpha]_D^{20}$ −67.6 (*c* 1.04, EtOH). IR: ν_{max} 3417, 2957, 1716, 1672, 1621, 1483, 1368, 1156, and 1097. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6, rt: rotamers ratio cannot be determined): 1.40 [9H, s, OC(CH_3)$_3$]; 1.55–2.30 [4H, m, CH_2 pyrrolidine]; 2.81 and 3.00 [2H, AB part of an ABX system, CH_2CO, J_{AB}=13.1, J_{AX}=5.8, J_{BX}=8.7]; 3.92–5.08 [7H, m, CH_2Ph, CH_2O, C*H* pyrrolidine, C*H*NHBoc]; 7.16–7.34 [5H, m, aromatics]; 7.54 [1H, br s, N*H*Boc]; 8.17 [1H, br t, N*H*CH$_2$Ph, *J*=5.6]. ^{13}C NMR (75 MHz): 26.7, 28.8, and 29.0 [2C, *C*H$_2$ pyrrolidine]; 28.0 [3C, OC(*C*H$_3$)$_3$]; 38.0 (*m*) and 38.1 (*M*), 41.7 [2C, NH*C*H$_2$Ph, *C*H$_2$CO]; 54.7, 55.8, and 62.2 [3C, *C*H pyrrolidine, *C*HNHBoc]; 69.6 [*C*H$_2$O]; 78.8 [O*C*(CH$_3$)$_3$]; 126.6 [*C*H *para* (Ph)]; 126.9 [2C, *C*H *ortho* (Ph)]; 128.2 [2C, *C*H *meta* (Ph)]; 139.3 [*C* (Ph)]; 154.8 [*C*O (Boc)]; 167.7, 170.8, and 171.5 [3C, *C*O].

4.13. General procedure for Jones oxidation and methyl ester formation

(a) Jones oxidation: a solution of the appropriate alcohol (53.42 mmol) was dissolved in dry acetone (5 ml) and cooled to 0 °C; then Jones reagent was added dropwise (3 M equiv) and the solution stirred at 0 °C for 2–3 h until disappearance of the starting material. A too long reaction time must be avoided in order to get a satisfactory yield. MeOH was added to reduce excess reagent and the reaction was stirred additional 30 min at rt. After dilution with 5% NH_4HPO_4 saturated with NaCl, an extraction with AcOEt was performed. Due to the high affinity for the aqueous layer the extraction was completed with CH_2Cl_2/MeOH 1:1. After drying and solvent removal, the crude acid was used as such for the following esterification. (b) Methyl ester formation: after dissolving the acid in THF (5 ml) and cooling to 0 °C, CH_2N_2 was added dropwise until the yellow color persisted. After addition of few drops of AcOH the solvent was distilled in vacuo and excess AcOH was azeotropically removed with heptane. The crude was directly purified by chromatography.

4.13.1. Compound ***32***

Chromatography with PE/AcOEt 3:7→15:85 gave **32** as a white foam in 75% overall yield. R_f 0.41 (PE/AcOEt 1:9, **C**). Anal. Found: C, 64.35; H, 6.35; N, 8.90. $C_{25}H_{29}N_3O_6$ requires C, 64.23; H, 6.25; N, 8.99. $[\alpha]_D^{20}$ +45.4 (*c* 1.32). IR: ν_{max} 3429, 3014, 1712, 1675, 1500, 1225, and 1075. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6, 62:38 mixture of rotamers even at 90 °C) at 90 °C: 1.84–2.56 [6H, m, CH_2 pyrrolidine, NCOCH_2]; 3.20–3.30 [2H, m, CH_2NHZ]; 3.64 (*M*) and 3.72 (*m*) [3H, 2s, OCH_3]; 4.28–4.72 [4H, m, C*H*, NHCH_2Ph]; 5.04 (*m*) and 5.05 (*M*) [2H, s, OCH_2Ph]; 6.66 (*M*) and 6.72 (*m*) [1H, br s, N*H*Z]; 7.20–7.39 [10H, m, aromatics]; 8.08 (*m*) [1H, br s, N*H*CH$_2$Ph (at rt: br t at 8.39, *J*=5.8)]; 8.39 (*m*) [1H, br s, N*H*CH$_2$Ph (at rt: br t at 8.70, *J*=5.8)]. ^{13}C NMR (75 MHz): 26.8 (*M*), 27.8 (*m*), 29.3 (*m*), and 30.3 (*M*) [2C, *C*H$_2$ pyrrolidine]; 33.5 (*M*) and 33.6 (*m*) [NCO*C*H$_2$]; 36.2 (*M*) and 36.4 (*m*) [*C*H$_2$NHZ]; 41.7 (*m*) and 42.2 (*M*) [NH*C*H$_2$Ph]; 51.8 (*M*) and 52.5 (*m*) [O*C*H$_3$]; 59.0 (*M*) and 59.4 (*m*), 60.16 (*m*) and 60.19 (*M*) [2C, *C*H pyrrolidine]; 65.2 [O*C*H$_2$Ph]; 126.6, 126.8, 127.1, 127.75, 127.71, 128.2, and 128.3 [10C, aromatic *C*H]; 137.1, 139.1 (*M*), and 139.4 (*m*) [2C, aromatic *C*]; 155.9 [*C*O (Z)]; 169.6 (*M*) and 169.8 (*m*), 171.1 (*M*) and 171.3 (*m*), 172.2 (*M*) and 172.5 (*m*) [3C, *C*O].

4.13.2. Compound ***33***

Chromatography with PE/AcOEt 1:9→AcOEt/Me$_2$CO 95:5 gave **32** as a yellow oil in 68% overall yield. R_f 0.23 (PE/AcOEt 1:9, **C**). Anal. Found: C, 64.20; H, 6.30; N, 8.85. $C_{25}H_{29}N_3O_6$ requires C, 64.23; H, 6.25; N, 8.99. $[\alpha]_D^{20}$ +16.71 (*c* 1.12). IR: ν_{max} 3440, 3005, 1725, 1653, 1189, and 1073. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6, rt: 71:29 mixture of rotamers, one highly prevailing at 90 °C) at 90 °C: 1.78–2.55 [6H, m, CH_2 pyrrolidine, NCOCH_2]; 3.26 [2H, center of m, CH_2NHZ]; 3.65 [3H, 2s, OCH_3]; 4.29–4.49 [4H, m, C*H*, NHCH_2Ph]; 5.04 [2H, s, OCH_2Ph]; 6.77 [1H, br s, N*H*Z]; 7.21–7.40 [10H, m, aromatics]; 8.20 [1H, br s, N*H*CH$_2$Ph (at rt: 2br t at 8.03 and 8.38, *J*=6.0, 6.0)]. ^{13}C NMR (75 MHz): 27.5 (*M*), 28.1 (*m*), 30.6 (*m*), and 30.7 (*M*) [2C, *C*H$_2$ pyrrolidine]; 33.4 (*M*) and 33.6 (*m*) [NCO*C*H$_2$]; 36.1 (*M*) and 36.4 (*m*) [*C*H$_2$NHZ]; 41.8 (*m*) and 42.3 (*M*) [NH*C*H$_2$Ph]; 52.4 (*M*) and 52.7 (*m*) [O*C*H$_3$]; 59.5 (*M*) and 59.6 (*m*), 61.4 (*m*) and 61.5 (*M*) [2C, *C*H pyrrolidine]; 65.2 [O*C*H$_2$Ph]; 126.68, 126.74, 126.9, 127.0, 127.7, 128.2, 128.3, and 128.4 [10C, aromatic *C*H]; 137.1, 138.7 (*M*), and 139.1 (*m*) [2C, aromatic *C*]; 155.9 [*C*O (Z)]; 170.3 (*M*) and 170.5 (*m*), 171.0 (*m*) and 171.1 (*M*), 173.4 (*m*) and 174.2 (*M*) [3C, *C*O].

*4.13.3. Compound **38***

Chromatography with PE/AcOEt 3:7→2:8 gave **38** as a pale yellow oil in 33% overall yield. R_f 0.50 (PE/AcOEt 2:8, **A** and **C**). Anal. Found: C, 62.00; H, 6.45; N, 9.65. $C_{30}H_{38}N_4O_8$ requires C, 61.84; H, 6.57; N, 9.62. $[\alpha]_D^{20}$ +41.9 (*c* 1.00). IR: ν_{max} 3431, 3001, 1712, 1660, 1491, 1425, 1369, 1215, and 1070. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6, rt: four rotamers can be detected with the two highly prevailing (≈80%) in a 58:41 ratio; a mixture of rotamers with very broad signals is present even at 120 °C): 1.39 and 1.41 [9H, 2s, C(CH_3)$_3$]; 1.78–4.77 [11H, m, CH_2 pyrrolidine, NHCH_2Ph, CH_2OH, CH_2NHZ, C*H*]; 3.58 and 3.74 [3H, 2s, OCH_3]; 4.97–5.10 [2H, m, OCH_2Ph]; 6.88 and 7.11 [1H, 2br d, N*H*Z, *J*=8.1, 7.2]; 6.90 and 7.05 [1H, 2br t, *NH*Boc, *J*=5.4, 5.7]; 7.20–7.39 [10H, m, aromatics]; 8.09 and 8.69 [1H, 2br t, N*H*CH$_2$Ph, *J*=5.8, 5.4)]. ^{13}C NMR (75 MHz) (only the signals of the two highly prevailing rotamers have been reported): 26.6 (*M*), 27.6 (*m*), 29.4 (*M*), and 30.5 (*m*) [2C, *C*H$_2$ pyrrolidine]; 27.95 (*m*) and 28.03 (*M*) [3C, OC(*C*H$_3$)$_3$]; 41.1, 41.8, and 42.5 [2C, *C*H$_2$N]; 50.8 (*M*) and 51.4 (*m*) [*C*HNHBoc]; 51.6 (*M*) and 52.6 (*m*) [OCH_3]; 59.3, 60.1 (*M*), and 60.5 (*m*) [2C, *C*H pyrrolidine]; 65.2 (*m*) and 65.3 (*M*) [*C*H$_2$O]; 78.3 (*M*) and 78.7 (*m*) [O*C*(CH$_3$)$_3$]; 126.6, 126.7, 127.0, 127.2, 127.59, 127.62, 127.7, 128.18, and 128.24 [10C, aromatic *C*H]; 136.9 (*M*) and 137.0 (*m*), 139.1 (*M*) and 139.2 (*m*) [2C, aromatic *C*]; 155.1, 155.6, and 156.0 [2C, *C*O (Z, Boc)]; 169.8, 169.9, 170.6, 171.2, 171.6, and 172.2 [3C, *C*O].

*4.13.4. Compound **39***

Chromatography with PE/AcOEt 3:7 gave **39** as a pale yellow oil in 27% overall yield. R_f 0.45 (PE/AcOEt 3:7, **A** and **C**). Anal. Found: C, 61.80; H, 6.60; N, 9.75. $C_{30}H_{38}N_4O_8$ requires C, 61.84; H, 6.57; N, 9.62. $[\alpha]_D^{20}$ +2.18 (*c* 1.05). IR: ν_{max} 3427, 2996, 1722, 1659, 1488, 1419, 1368, 1246, 1155, and 1074. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6, rt: five rotamers can be detected with the two highly prevailing (≈80%) in a 64:36 ratio; a mixture of rotamers with very broad signals is present even at 120 °C): 1.366 and 1.373 [9H, 2s, C(CH_3)$_3$]; 1.58–4.66 [11H, m, CH_2 pyrrolidine, NHCH_2Ph, CH_2OH, CH_2NHZ, C*H*]; 3.36 and 3.44 [3H, 2s, OCH_3]; 4.91–5.16 [2H, m, OCH_2Ph]; 7.04 [1H, br d, N*H*Z one rotamer, *J*=7.2]; 7.10 [1H, br t, *NH*Boc one rotamer, *J*=5.8]; 7.15–7.40 [10H, m, aromatics, N*H*Z and N*H*Boc other rotamers]; 8.09 and 8.69 [1H, 2br t, N*H*CH$_2$Ph, *J*=5.8, 5.4]. ^{13}C NMR (75 MHz) (only the signals of the two highly prevailing rotamers have been reported): 26.9 (*M*), 27.3 (*m*), 29.8 (*m*), and 30.4 (*M*) [2C, *C*H$_2$ pyrrolidine]; 27.8 (*m*) and 28.0 (*M*) [3C, OC(*C*H$_3$)$_3$]; 41.3, 41.5, 41.8, and 42.8 [2C, *C*H$_2$N]; 51.6 (*m*) and 52.1 (*M*) [*C*HNHBoc]; 51.8 (*M*) and 52.8 (*m*) [OCH_3]; 59.7 (*m*), 60.3 (*M*), 61.1 (*M*), and 61.8 (*M*) [2C, *C*H pyrrolidine]; 65.4 [*C*H$_2$O]; 78.6 (*M*) and 79.0 (*m*) [O*C*(CH$_3$)$_3$]; 126.58, 126.64, 126.75, 126.84, 127.2, 127.6, 127.67, 127.74, 128.1, 128.2, and 128.3 [10C, aromatic *C*H]; 136.79 (*m*) and 136.84 (*M*), 138.6 (*M*) and 139.1 (*m*) [2C, aromatic *C*]; 155.2 (*M*), 155.4 (*m*), and 156.2 [2C, *C*O (Z, Boc)]; 169.8 (*M*), 170.3 (*m*), 170.6 (*M*), 170.8 (*m*), 172.6 (*M*), and 173.2 (*m*) [3C, *C*O].

*4.14. Formation of bicyclic derivatives **40** and **41***

These compounds were obtained through the Jones oxidation of alcohols **36** and **37** (see Section 4.13), together with the expected carboxylic acids and have been separated from methyl esters **38** and **39** as described above.

*4.14.1. (3S,6R,8aR)-N-Benzyl-3-{[(benzyloxycarbonyl)-amino]methyl}-2-(tert-butoxycarbonyl)-octahydro-1,4-dioxo-pyrrolo[1,2-a]pyrazine-6-carboxamide **40***

Compound **40**, as a pale yellow oil, was obtained in 45% yield. R_f 0.35 (PE/AcOEt 2:8, **A** and **C**). Anal. Found: C, 63.40; H, 6.35; N, 10.25. $C_{29}H_{34}N_4O_7$ requires C, 63.26; H, 6.22; N, 10.18. $[\alpha]_D^{20}$ +115.5 (*c* 1.39). IR: ν_{max} 3430, 3353, 3002, 1780, 1723, 1671, 1370, 1192, and 1145. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6): 1.42 [9H, s C(CH_3)$_3$]; 1.69–2.25 [4H, m, CH_2 pyrrolidine]; 3.49 [2H, center of m, CH_2NHZ; at 90 °C: AB part of an ABX system at 3.53 and 3.61, J_{AB}=9.4, J_{AX}=4.2, J_{BX}=4.0]; 4.23–4.31 [2H, m, NHCH_2Ph; at 90 °C: AB part of an ABX system at 4.32 and 4.35, J_{AB}=15.3, J_{AX}=5.9, J_{BX}=5.8]; 4.37 and 4.48 [2H, 2t, C*H* pyrrolidine, *J*=7.5, 7.8]; 4.67 [1H, t, C*H*NHBoc, *J*=6.6]; 4.88 and 4.93 [2H, AB system, OCH_2Ph, J_{AB}=12.6]; 7.22–7.33 [10H, m, aromatics]; 7.59 [1H, br t, N*H*Z, *J*=6.3]; 8.28 [1H, br t, N*H*Bn, *J*=6.0]. ^{13}C NMR (75 MHz): 27.4 [3C, OC(*C*H$_3$)$_3$]; 27.7 and 28.0 [2C, *C*H$_2$ pyrrolidine]; 41.2 [*C*H$_2$NHZ]; 41.8 [NH*C*H$_2$Ph]; 59.8 and 60.3 [2C, *C*H pyrrolidine]; 60.1 [*C*HNHBoc]; 65.6 [*C*H$_2$O]; 83.2 [O*C*(CH$_3$)$_3$]; 126.6, 126.7, 127.7, 127.8, 128.16, and 128.25 [10C, aromatic *C*H]; 136.6 and 139.2 [2C, aromatic *C*]; 149.8 [*C*O (Boc)]; 156.6 [2C, *C*O (Z)]; 163.5 and 166.3 [2C, *C*O ring]; 170.2 [*C*ONHBn].

*4.14.2. Stereoisomer (3S,6S,8aR) **41***

Compound **41**, as a pale yellow oil, was obtained in 31% yield. R_f 0.35 (PE/AcOEt 3:7, **A** and **C**). Anal. Found: C, 63.35; H, 6.30; N, 10.30. $C_{29}H_{34}N_4O_7$ requires C, 63.26; H, 6.22; N, 10.18. $[\alpha]_D^{20}$ +53.8 (*c* 0.72). IR: ν_{max} 3441, 3018, 2987, 1781, 1727, 1675, 1370, 1249, 1145, and 1051. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6): 1.46 [9H, s C(CH_3)$_3$]; 1.85–2.16 [4H, m, CH_2 pyrrolidine]; 3.51 [2H, center of m, CH_2NHZ]; 4.25 and 4.31 [2H, AB part of an ABX system, NHCH_2Ph, J_{AB}=15.9, J_{AX}=5.8, J_{BX}=5.6]; 4.36 [1H, br d, C*H* pyrrolidine, *J*=8.4]; 4.52 [1H, br dd, C*H* pyrrolidine, *J*=9.8, 5.8]; 4.71 [1H, t, C*H*NHBoc, *J*=6.8]; 5.02 [2H, s, OCH_2Ph]; 7.21–7.40 [10H, m, aromatics]; 7.63 [1H, br t, N*H*Z, *J*=6.3]; 8.62 [1H, br t, N*H*Bn, *J*=6.0]. ^{13}C NMR (75 MHz): 26.9 and 28.6 [2C, *C*H$_2$ pyrrolidine]; 27.4 [3C, OC(*C*H$_3$)$_3$]; 40.7 [*C*H$_2$NHZ]; 41.9 [NH*C*H$_2$Ph]; 58.7, 59.6, and 60.4 [3C, *C*H pyrrolidine, *C*HNHBoc]; 65.5 [*C*H$_2$O]; 83.2 [O*C*(CH$_3$)$_3$]; 126.7, 126.9, 127.7, 127.8, 128.2, and 128.3 [10C, aromatic *C*H]; 136.8 and 139.1 [2C, aromatic *C*];

149.8 [*C*O (Boc)]; 156.2 [*C*O (Z)]; 163.2 and 166.6 [2C, *C*O ring]; 170.3 [*C*ONHBn].

4.15. General procedure for diazepine-1,5-dione ring formation

(a) Carbobenzyloxy group removal: a solution of the substrate in MeOH was treated with Pd/C (5–10% w/w) and hydrogenated for 1–3 h. After catalyst filtration and solvent removal, crude amine was used as such for the following reaction. (b) Cyclization: a solution of crude amine in dry ^{t}BuOH ($\approx$0.2 M) was refluxed for 38–45 h, in some cases (preparation of **34**, **35**, **42**, and **43**) in the presence of Et_3N (concentration in the reaction medium: 0.5 M). Solvent removal under reduced pressure was directly followed by chromatography.

*4.15.1. (7R,9aR)-N-Benzyl-octahydro-1,5-dioxo-1H-pyrrolo[1,2-a][1,4]diazepine-7-carboxamide **34***

Chromatography with CH_2Cl_2/MeOH 9:1→8:2 gave **34** as a white solid in 76% overall yield. R_f 0.35 (CH_2Cl_2/MeOH 9:1, **B**). Anal. Found: C, 63.65; H, 6.40; N, 13.75. $C_{16}H_{19}N_3O_3$ requires C, 63.77; H, 6.36; N, 13.94. $[\alpha]_D^{20}$ +38.4 (*c* 0.74, CH_2Cl_2/MeOH 9:1). Mp: 239.4–241.0 °C (CH_2Cl_2/MeOH). IR (KBr): ν_{max} 3235, 1684, 1653, 1621, 1564, 1435, 1395, and 1034. GC–MS: t_R 12.21; *m/z* 301 (M^+, 30), 168 (48), 167 (100), 139 (7.7), 126 (5.8), 125 (30), 122 (11), 113 (28), 106 (34), 97 (18), 96 (10), 91 (52), 70 (9.7), 69 (15), 68 (66), 65 (9.2), 55 (18), 43 (6.7), 42 (5.0), 41 (16), 39 (6.0). ^{1}H NMR (300 MHz, DMSO-d_6): 1.76–2.00 [3H, m, CH_2C*H*H pyrrolidine]; 2.37–2.49 [2H, m, CH_2C*H*H pyrrolidine, CONHCH$_2$C*H*H]; 2.73 [1H, dt, CONHCH$_2$C*H*H, *J*=17.7, 3.8]; 3.03–3.14 [1H, m, CONHC*H*HCH$_2$]; 3.70 [1H, center of m, CONHCH*H*CH$_2$]; 4.27 and 4.32 [2H, AB part of an ABX system, CH_2Ph, J_{AB}=13.8, J_{AX}=4.1, J_{BX}=3.4]; 4.44 [1H, dd, C*H*CONHBn, *J*=7.2, 1.2]; 4.92 [1H, br d, C*H*CONHCH$_2$, *J*=5.7]; 7.20–7.34 [5H, m, aromatics]; 7.98 [1H, br t, N*H*CH$_2$CH$_2$, *J*=5.6]; 8.44 [1H, br t, N*H*CH$_2$Ph, *J*=5.8]. ^{13}C NMR (75 MHz): 25.6 and 27.6 [2C, *C*H$_2$ pyrrolidine]; 35.8 [CONH*C*H$_2$CH$_2$]; 36.7 [CONHCH$_2$*C*H$_2$]; 41.8 [NH*C*H$_2$Ph]; 56.2 [*C*HCONHCH$_2$]; 61.7 [*C*HCONHBn]; 126.6 [*C*H *para* of Ph]; 126.7 [2C, *C*H *ortho* of Ph]; 128.2 [2C, *C*H *meta* of Ph]; 139.4 [aromatic *C*]; 168.8, 171.1, and 171.2 [3C, *C*O].

*4.15.2. Stereoisomer (7S,9aR) **35***

Chromatography with CH_2Cl_2/MeOH 9:1→8:2 gave **35** as a white solid in 70% overall yield. R_f 0.35 (CH_2Cl_2/MeOH 9:1, **B**). Anal. Found: C, 63.85; H, 6.45; N, 13.80. $C_{16}H_{19}N_3O_3$ requires C, 63.77; H, 6.36; N, 13.94. $[\alpha]_D^{20}$ −25.20 (*c* 0.36, CH_2Cl_2/MeOH 9:1). Mp: 230.8–233.8 °C (CH_2Cl_2/MeOH). IR (KBr): ν_{max} 3272, 1699, 1651, 1609, 1557, 1440, 1397, 1322, 1292, 1241, and 1208. GC–MS: t_R 12.40; *m/z* 301 (M^+, 27), 169 (5.5), 168 (53), 167 (100), 139 (9.4), 126 (6.5), 125 (33), 122 (12), 113 (30), 106 (39), 97 (20), 96 (11), 92 (5.4), 91 (60), 77 (5.1), 70 (10), 69 (17), 68 (72), 65 (11), 56 (6.2), 55 (20), 43 (6.7), 42 (5.5), 41 (17), 39 (6.5). ^{1}H NMR (300 MHz, DMSO-d_6): 1.81–2.05 [3H, m, CH_2C*H*H pyrrolidine]; 2.34–2.48 [2H, m, CH_2C*H*H pyrrolidine, CONHCH$_2$C*H*H]; 2.69 [1H, ddd, CONHCH$_2$C*H*H, *J*=17.1, 5.4, 3.0]; 3.06–3.18 [1H, m, CONHC*H*HCH$_2$]; 3.59 [1H, center of m, CONHCH*H*CH$_2$]; 4.22 and 4.29 [2H, AB part of an ABX system, CH_2Ph, J_{AB}=15.4, J_{AX}=5.6, J_{BX}=5.8]; 4.49 [1H, dd, C*H*CONHBn, *J*=8.4, 2.7]; 4.70 [1H, t, C*H*CONHCH$_2$, *J*=7.5]; 7.19–7.34 [5H, m, aromatics]; 7.96 [1H, br t, N*H*CH$_2$CH$_2$, *J*=5.1]; 8.29 [1H, br t, N*H*CH$_2$Ph, *J*=5.8]. ^{13}C NMR (75 MHz): 26.7 and 27.2 [2C, *C*H$_2$ pyrrolidine]; 36.0 [CONH*C*H$_2$CH$_2$]; 36.4 [CONHCH$_2$*C*H$_2$]; 41.8 [NH*C*H$_2$Ph]; 57.7 [*C*HCONHCH$_2$]; 61.0 [*C*HCONHBn]; 126.5 [*C*H *para* of Ph]; 126.8 [2C, *C*H *ortho* of Ph]; 128.1 [2C, *C*H *meta* of Ph]; 139.5 [aromatic *C*]; 169.1, 170.1, and 171.0 [3C, *C*O].

*4.15.3. (4S,7R,9aR)-N-Benzyl-4-[(tert-butoxycarbonyl)-amino]-octahydro-1,5-dioxo-1H-pyrrolo[1,2-a][1,4]-diazepin-7-carboxamide **42***

This compound has been prepared by the hydrogenolysis–cyclization procedure from: (a) purified **38** (65%); (b) purified **40** (48%); (c) a one-pot procedure (56% from **36**). Chromatography with CH_2Cl_2/MeOH 95:5 gave **42** as a white solid. R_f 0.33 (CH_2Cl_2/MeOH 93:7, **A** and **B**). Anal. Found: C, 60.65; H, 6.75; N, 13.60. $C_{21}H_{28}N_4O_5$ requires C, 60.56; H, 6.78; N, 13.45. $[\alpha]_D^{20}$ +93.1 (*c* 0.52, CH_2Cl_2/MeOH 9:1) from (a) and $[\alpha]_D^{20}$ +95.1 (*c* 0.41, CH_2Cl_2/MeOH 9:1) from (b). Mp: 198.1–199.7 °C (CH_2Cl_2/MeOH). IR (KBr): ν_{max} 3310, 2973, 1684, 1546, 1491, 1444, 1367, 1251, 1166, and 1061. GC–MS: unsuitable for this analysis. HPLC–MS (exact mass 416.2): *m/z* 417.1 (M^++H), 439.1 (M^++Na), 455.1 (M^++K), 855.0 ($2M^+$+Na); MS^2 (417.1): 361.1, 317.0. ^{1}H NMR (300 MHz, DMSO-d_6) at 90 °C: 1.43 [9H, s, C(CH_3)$_3$]; 1.81–2.10 [3H, m, CH_2C*H*H pyrrolidine]; 2.49–2.58 [1H, m, CH_2C*H*H pyrrolidine]; 3.12 [1H, ddd, C*H*HCHNHBoc, *J*=13.8, 8.4, 3.6]; 3.62 [1H, dt, CH*H*CHNHBoc, *J*=13.5, 4.5]; 4.31 [2H, d, CH_2Ph, *J*=6.3]; 4.46 [1H, dd, C*H*CONHBn, *J*=8.1, 2.4]; 4.73 [1H, ddd, C*H*NHBoc, *J*=12.3, 7.2, 4.5]; 4.88 [1H, dd, C*H*CONHCH$_2$, *J*=7.8, 2.1]; 6.42 [1H, br d, N*H*Boc, *J*=6.0 (at rt: d at 6.93, *J*=7.5)]; 7.20–7.34 [5H, m, aromatics]; 7.53 [1H, br s, N*H*CH$_2$CH (at rt: br s at 7.83)]; 8.13 [1H, br s, N*H*CH$_2$Ph (at rt: br t at 8.44, *J*=6.0)]. ^{13}C NMR (75 MHz): 25.7 and 28.0 [2C, *C*H$_2$ pyrrolidine]; 28.1 [3C, OC(*C*H$_3$)$_3$]; 41.8 [NH*C*H$_2$Ph]; 43.6 [CONH*C*H$_2$CH]; 51.8 [*C*HNHBoc]; 58.1 [*C*HCONHCH$_2$]; 61.4 [*C*HCONHBn]; 78.3 [O*C*(CH$_3$)$_3$]; 126.6 [*C*H *para* of Ph]; 126.7 [2C, *C*H *ortho* of Ph]; 128.2 [2C, *C*H *meta* of Ph]; 139.3 [aromatic *C*]; 154.8 [*C*O (Boc)]; 168.3, 169.6, and 170.8 [3C, *C*O].

*4.15.4. Stereoisomer (4S,7S,9aR) **43***

This compound has been prepared by the hydrogenolysis–cyclization procedure from: (a) purified **39** (66%); (b) purified **41** (49%); (c) a one-pot procedure (46% from **37**). Chromatography with CH_2Cl_2/MeOH 93:7→9:1 gave **43** as a white solid. R_f 0.30 (CH_2Cl_2/MeOH 93:7, **A** and **B**). Anal. Found: C, 60.70; H, 6.85; N, 13.55. $C_{21}H_{28}N_4O_5$ requires C, 60.56; H, 6.78; N, 13.45. $[\alpha]_D^{20}$ +2.8 (*c* 0.50, CH_2Cl_2/MeOH 9:1) from

(a) and $[\alpha]_D^{20}$ +2.2 (*c* 0.63, CH_2Cl_2/MeOH 9:1) from (b). Mp: 130.1–132.3 °C (CH_2Cl_2/MeOH). IR (KBr): ν_{max} 3320, 2974, 1692, 1493, 1435, 1367, 1241, 1171, 1062, and 1028. GC–MS: unsuitable for this analysis. HPLC–MS (exact mass 416.2): *m/z* 417.1 (M^++H), 439.2 (M^++Na), 455.1 (M^++K), 833.0 ($2M^+$+H), 855.2 ($2M^+$+Na); MS^2 (417.1): 361.1, 317.1. ^{1}H NMR (300 MHz, DMSO-d_6) at 90 °C: 1.42 [9H, s, C(C*H*$_3$)$_3$]; 1.84–2.10 [3H, m, C*H*$_2$C*H*H pyrrolidine]; 2.36–2.47 [1H, m, CH_2CH*H* pyrrolidine]; 3.19 [1H, ddd, C*H*HCHNHBoc, *J*=13.2, 9.6, 2.7]; 3.43 [1H, ddd, CH*H*CHNHBoc, *J*=13.5, 4.8, 3.9]; 4.27 and 4.32 [2H, AB part of an ABX system, C*H*$_2$Ph, J_{AB}=15.5, J_{AX}=5.9, J_{BX}=6.3]; 4.54 [1H, dd, C*H*CONHBn, *J*=8.4, 4.5]; 4.34 [1H, ddd, C*H*NHBoc, *J*=9.9, 7.2, 3.3]; 4.76 [1H, t, C*H*CONHCH$_2$, *J*=7.0]; 6.49 [1H, br s, N*H*Boc (at rt: d at 7.09, *J*=7.8)]; 7.20–7.34 [5H, m, aromatics]; 7.54 [1H, br s, N*H*CH$_2$CH (at rt: br t at 7.86, *J*=3.8)]; 8.02 [1H, br s, N*H*CH$_2$Ph (at rt: br t at 8.32, *J*=6.2)]. ^{13}C NMR (75 MHz): 27.0 and 27.6 [2C, *C*H$_2$ pyrrolidine]; 28.1 [3C, OC(*C*H$_3$)$_3$]; 41.8 [NH*C*H$_2$Ph]; 43.2 [CONH*C*H$_2$CH]; 51.8 [*C*HNHBoc]; 58.7 [*C*HCONHCH$_2$]; 61.2 [*C*HCONHBn]; 78.3 [O*C*(CH$_3$)$_3$]; 126.5 [*C*H *para* of Ph]; 126.7 [2C, *C*H *ortho* of Ph]; 128.1 [2C, *C*H *meta* of Ph]; 139.3 [aromatic *C*]; 154.9 [*C*O (Boc)]; 168.7, 168.9, and 170.6 [3C, *C*O].

4.15.5. (7R,9aR)-7-{[(tert-Butyldimethylsilyl)oxy]methyl}-hexahydro-2H-pyrrolo[1,2-a][1,4]diazepine-1,5-dione **58**

Chromatography with CH_2Cl_2/MeOH 99:1→95:5 gave **58** as a pale yellow oil in 98% overall yield. R_f 0.31 (CH_2Cl_2/MeOH 95:5, **B**). Anal. Found: C, 57.80; H, 9.15; N, 8.80. $C_{15}H_{28}N_2O_3Si$ requires C, 57.66; H, 9.03; N, 8.96. $[\alpha]_D^{20}$ +65.0 (*c* 1.02). IR: ν_{max} 3414, 3004, 2948, 1682, 1620, 1390, 1189, 1108, and 1045. GC–MS: t_R 9.48; *m/z* 312 (M^+, 0.058), 257 (5.8), 256 (19), 255 (100), 167 (8.8), 156 (21), 82 (6.2), 75 (13), 73 (11), 68 (8.6), 55 (6.3). ^{1}H NMR (300 MHz, DMSO-d_6): 0.03 and 0.04 [6H, 2s, Si(C*H*$_3$)$_2$]; 0.86 [9H, s, SiC(C*H*$_3$)$_3$]; 1.60–2.08 [3H, m, C*H*$_2$C*H*H pyrrolidine]; 2.34–2.46 [2H, m, CH_2CH*H* pyrrolidine, CONHCH$_2$C*H*H]; 2.72 [1H, dt, CONHCH$_2$CH*H*, *J*=17.4, 4.2]; 3.05 [1H, center of m, CONHC*H*HCH$_2$]; 3.49 and 3.69 [2H, AB part of an ABX system, C*H*$_2$O, J_{AB}=9.6, J_{AX}=7.5, J_{BX}=3.3]; 3.60 [1H, ddd, CONHCH*H*CH$_2$, *J*=15.6, 7.5, 4.5]; 4.06 [1H, dt, C*H*CH$_2$O, *J*=7.5, 3.3]; 4.73 [1H, d, C*H*CONH, *J*=8.4]; 7.90 [1H, br t, N*H*, *J*=5.1]. ^{13}C NMR (75 MHz): −5.5 [2C, Si(*C*H$_3$)$_2$]; 17.8 [Si*C*(CH$_3$)$_3$]; 24.6 and 24.7 [2C, *C*H$_2$ pyrrolidine]; 25.7 [3C, SiC(*C*H$_3$)$_3$]; 35.9 [CONH*C*H$_2$CH$_2$]; 36.7 [CONHCH$_2$*C*H$_2$]; 55.9 [*C*HCONHCH$_2$]; 60.0 [*C*HCH$_2$O]; 61.5 [*C*H$_2$O]; 168.4 and 171.1 [2C, *C*O].

4.15.6. Stereoisomer (7S,9aR) **59**

Chromatography with CH_2Cl_2/MeOH 99:1→95:5 gave **59** as a pale yellow solid in 86% overall yield. R_f 0.32 (CH_2Cl_2/MeOH 95:5, **B**). Anal. Found: C, 57.75; H, 8.90; N, 8.85. $C_{15}H_{28}N_2O_3Si$ requires C, 57.66; H, 9.03; N, 8.96. $[\alpha]_D^{20}$ +6.4 (*c* 0.46). Mp: 102.6–104.0 °C (CH_2Cl_2/MeOH). IR: ν_{max} 3410, 3003, 2950, 1651, 1418, 1393, and 1096. GC–MS: t_R 9.58; *m/z* 297 (M^+−15, 2.6), 257 (5.4), 256 (19), 255 (100), 167 (6.8), 156 (29), 125 (5.9), 113 (6.0), 99 (5.1), 97 (6.9), 82 (15), 80 (6.1), 75 (35), 73 (32), 68 (23), 59 (16), 58 (5.7), 57 (6.8), 56 (6.8), 55 (23), 47 (5.2), 45 (8.4), 43 (8.7), 42 (7.8), 41 (20), 39 (5.0). ^{1}H NMR (300 MHz, DMSO-d_6): 0.01 [6H, s, Si(C*H*$_3$)$_2$]; 0.86 [9H, s, SiC(C*H*$_3$)$_3$]; 1.70–1.91 [3H, m, C*H*$_2$C*H*H pyrrolidine]; 2.33–2.46 [2H, m, CH_2CH*H* pyrrolidine, CONHCH$_2$C*H*H]; 2.66 [1H, ddd, CONHCH$_2$CH*H*, *J*=17.4, 5.7, 3.0]; 3.06 [1H, dq, CONHC*H*HCH$_2$, *J*=15.3, 5.1]; 3.31 and 3.58 [2H, AB part of an ABX system, C*H*$_2$O, J_{AB}=8.8, J_{AX}=8.2, J_{BX}=5.0]; 3.58 [1H, center of m, CONHCH*H*CH$_2$]; 4.14 [1H, br dt, C*H*CH$_2$O, *J*=7.4, 2.7]; 4.64 [1H, dd, C*H*CONH, *J*=9.0, 7.5]; 7.95 [1H, br t, N*H*, *J*=5.0]. ^{13}C NMR (75 MHz): −5.5 [2C, Si(*C*H$_3$)$_2$]; 17.9 [Si*C*(CH$_3$)$_3$]; 24.2 and 25.5 [2C, *C*H$_2$ pyrrolidine]; 25.7 [3C, SiC(*C*H$_3$)$_3$]; 36.0 [CONH*C*H$_2$CH$_2$]; 36.6 [CONHCH$_2$*C*H$_2$]; 57.0 [*C*HCONHCH$_2$]; 59.3 [*C*HCH$_2$O]; 61.8 [*C*H$_2$O]; 169.0 and 170.6 [2C, *C*O].

4.16. Boc introduction on compounds **14** and **15h**

A solution of **14h** or **15h** (678 mg, 1.19 mmol) in dry CH_2Cl_2 (18 ml) was cooled to 0 °C and treated with Et_3N (249 μl, 1.79 mmol), di-*tert*-butyl dicarbonate (287 μl, 1.25 mmol), and DMAP (22 mg, 17.85 μmol). After 10 min the reaction was allowed to stir at rt and, after 3.5 h, usually an addition of a substoichiometric amount of all the reagents was necessary (0.2–0.5 M equiv). After stirring overnight the solvent was evaporated and the crude was directly purified by chromatography.

4.16.1. Compound **56**

Chromatography with PE/AcOEt 8:2→1:1 gave **56** as an orange foam in 85% yield. R_f 0.71 (PE/AcOEt 1:1, **A** and **C**). Anal. Found: C, 62.90; H, 7.80; N, 6.30. $C_{35}H_{51}N_3O_8Si$ requires C, 62.75; H, 7.67; N, 6.27. $[\alpha]_D^{20}$ +59.9 (*c* 1.20). IR: ν_{max} 3447, 2949, 1711, 1626, 1239, 1148, 1084, and 833. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6, rt: 67:33 mixture of rotamers, remains even at 90 °C) at 90 °C: 0.03, 0.055, and 0.065 [6H, 3s, Si(C*H*$_3$)$_2$]; 0.89 [9H, s, SiC(C*H*$_3$)$_3$]; 1.39 and 1.40 [2H, 2s, OC(C*H*$_3$)$_3$]; 1.83–2.58 [6H, m, C*H*$_2$ pyrrolidine, NCOC*H*$_2$]; 3.25 [2H, center of m, C*H*$_2$NHZ]; 3.54–3.79 [2H, m, CHC*H*$_2$OSi]; 3.78 [3H, s, OC*H*$_3$]; 4.02–4.10 [1H, m, C*H*CH$_2$OSi]; 5.04 and 5.04 [2H, AB system, OC*H*$_2$Ph, *J*=13.2]; 5.10 (*M*) and 5.40 (*m*) [1H, 2d, C*H*CONH, *J*=9.0 both]; 6.68 and 6.78 [1H, 2br s, N*H*Z, (at rt: 2br t at 7.15 and 7.21, *J*=5.7, 6.0)]; 6.92 [2H, dt, C*H meta* to OMe, *J*=9.0, 2.7]; 7.07 [2H, apparent d, C*H ortho* to OMe, *J*=8.7]; 7.27–7.38 [5H, m, aromatics]. ^{13}C NMR (75 MHz): −5.6, −5.5, and −5.4 [2C, Si(*C*H$_3$)$_2$]; 17.8 [*C*(CH$_3$)$_3$]; 24.5 (*m*), 26.7 (*M*), 27.1 (*M*), and 29.5 (*m*) [2C, *C*H$_2$ pyrrolidine]; 25.7 [3C, SiC(*C*H$_3$)$_3$]; 27.4 [3C, OC(*C*H$_3$)$_3$]; 33.6 (*M*) and 34.1 (*m*) [NCO*C*H$_2$]; 36.6 (*m*) and 36.7 (*M*) [*C*H$_2$NHZ]; 55.2 [O*C*H$_3$]; 59.0 (*M*) and 59.1 (*m*) [*C*HCH$_2$OSi]; 60.5 (*M*) and 62.0 (*m*) [*C*HCONH]; 64.3 [*C*H$_2$OSi]; 65.1 [O*C*H$_2$Ph]; 82.8 (*M*) and 83.4 (*m*), 113.8 (*M*) and 113.9 (*m*) [2C, *C*H *ortho* to OMe]; 127.6, 127.7, and 128.2 [5C, *C*H of Ph]; 129.1 (*M*) and 129.2 (*m*) [2C, *C*H *meta* to OMe]; 130.9 (*m*) and 131.4 (*M*)

[*C*-NBoc]; 137.0 [*C* of Ph]; 151.9 (*m*) and 152.3 (*M*), 155.9, 158.2 (*M*) and 158.4 (*m*) [2C, *C*-OMe, *C*O (Z, Boc)]; 169.4 (*M*) and 169.6 (*m*), 174.5 (*M*) and 174.6 (*m*) [2C, *C*O].

4.16.2. Compound **57**

Chromatography with PE/AcOEt 8:2→1:1 gave **57** as an orange oil in an estimated 55% (based on NMR) (73% on unrecovered **15h**) yield. An analytical sample of **57** was obtained through an additional chromatography. R_f 0.51 (PE/AcOEt 6:4, **A** and **C**). Anal. Found: C, 62.80; H, 7.60; N, 6.35. $C_{35}H_{51}N_3O_8Si$ requires C, 62.75; H, 7.67; N, 6.27. $[\alpha]_D^{20}$ −77.5 (*c* 0.91). IR: ν_{max} 3442, 3021, 1712, 1626, 1421, 1214, 1147, and 1087. GC–MS: unsuitable for this analysis. ^{1}H NMR (300 MHz, DMSO-d_6, rt: ≈3:1 mixture of rotamers) at 90 °C: 0.06 [6H, s, Si(CH_3)$_2$]; 0.89 [9H, s, SiC(CH_3)$_3$]; 1.39 [2H, s, OC(CH_3)$_3$]; 1.80–2.76 [6H, m, CH_2 pyrrolidine, NCOCH_2]; 3.28 [2H, br q, CH_2NHZ, *J*=6.4]; 3.55–4.10 [3H, m, C*H*CH_2OSi]; 3.80 [3H, s, OCH_3]; 5.00–5.40 [3H, m, OCH_2Ph, C*H*CONH]; 6.81 [1H, br s, N*H*Z, (at rt: br t at 7.22 (*M*), *J*=5.4)]; 6.94 [2H, dt, C*H* *meta* to OMe, *J*=9.0, 2.7]; 7.08 [2H, dt, C*H* *ortho* to OMe, *J*=8.7, 2.6]; 7.28–7.39 [5H, m, aromatics]. ^{13}C NMR (75 MHz): −5.6, −5.5, and −5.4 [2C, Si(*C*H$_3$)$_2$]; 17.8 [*C*(CH$_3$)$_3$]; 25.7 [3C, SiC(*C*H$_3$)$_3$]; 26.2 (*m*), 27.0 (*M*), 27.1 (*M*), and 29.4 (*m*) [2C, *C*H$_2$ pyrrolidine]; 27.4 [3C, OC(*C*H$_3$)$_3$]; 33.2 (*M*) and 33.7 (*m*) [NCO*C*H$_2$]; 36.4 (*m*) and 36.7 (*M*) [*C*H$_2$NHZ]; 55.2 [OCH$_3$]; 59.2 (*m*) and 59.5 (*M*) [*C*HCH$_2$OSi]; 61.0 (*M*) and 61.8 (*m*) [*C*HCONH]; 62.4 (*m*) and 63.1 (*M*) [*C*H$_2$OSi]; 65.1 [OCH$_2$Ph]; 82.7 (*M*) and 83.3 (*m*), 113.8 (*M*) and 113.9 (*m*) [2C, *C*H *ortho* to OMe]; 127.6 and 127.9 [5C, *C*H of Ph]; 129.0 (*M*) and 129.2 (*m*) [2C, *C*H *meta* to OMe]; 130.8 (*m*) and 131.4 (*M*) [*C*-NBoc]; 137.1 [*C* of Ph]; 151.9 (*m*) and 152.3 (*M*), 155.9, 158.2 (*M*) and 158.4 (*m*) [2C, *C*-OMe, *C*O (Z, Boc)]; 169.1 (*M*) and 169.3 (*m*), 175.0 (*m*) and 175.6 (*M*) [2C, *C*O].

4.17. TBDMS removal from **58** and **59**

A solution of **58** or **59** (150 mg, 48.00 μmol) in dry MeOH (3 ml) was cooled to 0 °C and then Amberlyst 15 (30 mg) was added. After 30 min the reaction was allowed to stir at rt for 4 h. The mixture was diluted with CH_2Cl_2/Me_2CO to solubilize the product. Solid $CaCO_3$ was added (≈100 mg) and, after stirring for additional 15 min, a rapid filtration removed all the solids. The solution was concentrated in vacuo and directly purified by chromatography.

4.17.1. (7R,9aR)-Hexahydro-7-(hydroxymethyl)-2H-pyrrolo[1,2-a][1,4]diazepine-1,5-dione **60**

Chromatography with CH_2Cl_2/Me_2CO/MeOH 4:4:2 gave **60** as a white solid in 93% yield. R_f 0.34 (CH_2Cl_2/Me_2CO/MeOH 4:4:2, **B**). Anal. Found: C, 54.50; H, 7.15; N, 14.25. $C_9H_{14}N_2O_3$ requires C, 54.53; H, 7.12; N, 14.13. $[\alpha]_D^{20}$ +41.8 (*c* 0.97, $CHCl_3$/MeOH 9:1). Mp: 178.5–180.1 °C (CH_2Cl_2/Me_2CO/MeOH). IR (KBr): ν_{max} 3379, 3257, 2937, 1679, 1610, 1452, 1409, 1168, 1116, and 1043. GC–MS: t_R 8.30; *m*/*z* 198 (M^+, 3.3), 180 (7.1), 168 (23), 167 (100), 139 (6.8), 128 (6.6), 125 (28), 122 (11), 113 (27), 100 (28), 97 (28), 96 (12), 82 (8.5), 72 (6.3), 70 (7.9), 69 (15), 68 (72), 57 (7.4), 56 (10), 55 (31), 44 (7.6), 43 (10), 42 (12), 41 (23), 39 (9.6). ^{1}H NMR (300 MHz, DMSO-d_6): 1.56–2.06 [3H, m, CH_2C*H*H pyrrolidine]; 2.32–2.44 [2H, m, CH$_2$CH*H* pyrrolidine, CONHCH$_2$C*H*H]; 2.73 [1H, dt, CONHCH$_2$CH*H*, *J*=17.4, 4.2]; 3.04 [1H, center of m, CONHC*H*HCH$_2$]; 3.24–3.54 [2H, m, CH$_2$O]; 3.61 [1H, center of m, CONHCH*H*CH$_2$]; 4.03 [1H, dt, C*H*CH$_2$O, *J*=7.6, 3.6]; 4.75 [1H, br d, C*H*CONH, *J*=8.1]; 4.79 [1H, t, O*H*, *J*=5.7]; 7.90 [1H, br t, N*H*, *J*=5.0]. ^{13}C NMR (75 MHz): 24.7 and 24.8 [2C, *C*H$_2$ pyrrolidine]; 35.9 [CONH*C*H$_2$CH$_2$]; 36.7 [CONHCH$_2$*C*H$_2$]; 55.9 [*C*HCONHCH$_2$]; 60.3 [*C*H$_2$O]; 60.6 [*C*HCH$_2$O]; 168.5 and 171.2 [2C, *C*O].

4.17.2. Stereoisomer (7S,9aR) **61**

Chromatography with CH_2Cl_2/Me_2CO/MeOH 4:4:2 gave **60** as a white solid in 93% yield. R_f 0.34 (CH_2Cl_2/Me_2CO/MeOH 4:4:2, **B**). Anal. Found: C, 54.65; H, 7.00; N, 14.00. $C_9H_{14}N_2O_3$ requires C, 54.53; H, 7.12; N, 14.13. $[\alpha]_D^{20}$ +8.3 (*c* 0.97, $CHCl_3$/MeOH 9:1). Mp: 200.9–202.6 °C (CH_2Cl_2/Me_2CO/MeOH). IR (KBr): ν_{max} 3319, 3231, 2975, 1675, 1612, 1453, 1406, 1167, 1122, 1066, and 1045. GC–MS: t_R 8.89; *m*/*z* 198 (M^+, 3.7), 180 (7.5), 168 (26), 167 (100), 128 (6.2), 125 (27), 122 (9.2), 113 (22), 100 (22), 97 (22), 96 (9.5), 82 (9.0), 70 (6.6), 69 (11), 68 (56), 57 (6.7), 56 (7.5), 55 (23), 44 (6.8), 43 (8.1), 42 (8.0), 41 (17), 39 (7.4). ^{1}H NMR (300 MHz, DMSO-d_6): 1.65–1.94 [3H, m, CH_2C*H*H pyrrolidine]; 2.31–2.45 [2H, m, CH$_2$CH*H* pyrrolidine, CONHCH$_2$C*H*H]; 2.64 [1H, ddd, CONHCH$_2$CH*H*, *J*=17.1, 5.1, 3.0]; 2.96–3.44 [3H, m, CONHC*H*HCH$_2$, CH_2O]; 3.59 [1H, center of m, CONHCH*H*CH$_2$]; 4.11 [1H, dt, C*H*CH$_2$O, *J*=8.0, 3.6]; 4.65 [1H, dd, C*H*CONH, *J*=9.3, 7.2]; 4.78 [1H, t, O*H*, *J*=5.7]; 7.96 [1H, br t, N*H*, *J*=5.1]. ^{13}C NMR (75 MHz): 24.1 and 25.1 [2C, *C*H$_2$ pyrrolidine]; 35.9 [CONH*C*H$_2$CH$_2$]; 36.6 [CONHCH$_2$*C*H$_2$]; 56.8 [*C*HCONHCH$_2$]; 59.9 [*C*HCH$_2$O]; 60.3 [*C*H$_2$O]; 168.9 and 170.8 [2C, *C*O].

4.18. General procedure for oxidation to carboxylic acid with PDC, followed by methyl ester or amide formation

(a) Oxidation: a solution of alcohol **60** or **61** (100 mg, 50.45 μmol) in dry DMF (2 ml) was cooled to 0 °C and then pyridinium dichromate (PDC, 569 mg, 1.51 mmol) was added. The resulting slurry was allowed to stir at rt for 20–26 h. After dilution with 1–2 ml of CH_2Cl_2, solid $Na_2S_2O_5$ was added and, after 30 min, the mixture was directly filtered over a silica column, using CH_2Cl_2/Me_2CO 6:4→CH_2Cl_2/Me_2CO/AcOH 3:6:1 as eluent. (b) Methyl ester: the general procedure described in Section 4.13 was followed, but, due to insolubility of the carboxylic acid in THF, DMF was employed. (c) Benzyl amide formation: the carboxylic acid from the previous reaction was partially solubilized in dry CH_2Cl_2/DMF (2:1; 6 ml). After cooling to 0 °C benzylamine (83 μl, 75.68 μmol), HATU [O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, 288 mg, 75.68 μmol], and 2,4,6-collidine (113 μl, 85.77 μmol) were added and the reaction was stirred at rt for 26 h. The solvents were

evaporated under reduced pressure and the crude was directly purified by chromatography.

4.18.1. (7R,9aR)-Methyl octahydro-1,5-dioxo-1H-pyrrolo-[1,2-a][1,4]diazepine-7-carboxylate **62**

Chromatography with CH_2Cl_2/MeOH 95:5→9:1 gave **62** as a pale yellow oil in 51% overall yield. R_f 0.36 (CH_2Cl_2/MeOH 9:1, **B**). Anal. Found: C, 53.15; H, 6.30; N, 12.25. $C_{10}H_{14}N_2O_4$ requires C, 53.09; H, 6.24; N, 12.38. $[\alpha]_D^{20}$ +69.5 (*c* 0.76). IR: ν_{max} 3411, 2997, 1740, 1680, 1629, 1389, 1171, and 1111. GC–MS: t_R 8.34; *m/z* 226 (M^+, 38), 168 (10), 167 (100), 139 (6.1), 129 (6.5), 128 (86), 125 (20), 122 (7.3), 113 (18), 112 (5.3), 100 (5.0), 97 (17), 96 (11), 70 (5.1), 69 (15), 68 (87), 55 (15), 43 (5.3), 42 (8.4), 41 (24), 39 (7.4). ^{1}H NMR (300 MHz, DMSO-d_6): 1.78–2.07 [3H, m, CH_2C*H*H pyrrolidine]; 2.37–2.47 [2H, m, CH_2CH*H* pyrrolidine, CONHCH_2C*H*H]; 2.72 [1H, dt, CONHCH_2CH*H*, *J*=18.0, 3.9]; 3.08 [1H, m, CONHC*H*HCH_2]; 3.63 [3H, s, OCH_3]; 3.69 [1H, center of m, CONHCH*H*CH_2]; 4.44 [1H, dd, C*H*CO_2Me, *J*=7.8, 2.7]; 4.90 [1H, dd, C*H*CONH, *J*=8.1, 3.3]; 8.02 [1H, br t, N*H*, *J*=5.1]. ^{13}C NMR (75 MHz): 25.8 and 26.5 [2C, *C*H_2 pyrrolidine]; 35.6 [CONH*C*H_2CH_2]; 36.2 [CONHCH_2*C*H_2]; 51.8 [*C*H_3]; 56.2 [*C*HCONHCH_2]; 60.2 [*C*HCH_2O]; 168.7, 170.7, and 172.0 [3C, *C*O].

4.18.2. Stereoisomer (7R,9aR) **63**

Chromatography with CH_2Cl_2/MeOH 95:5→9:1 gave **63** as a pale yellow oil in 31% overall yield. R_f 0.31 (CH_2Cl_2/MeOH 9:1, **B**). Anal. Found: C, 53.00; H, 6.35; N, 12.40. $C_{10}H_{14}N_2O_4$ requires C, 53.09; H, 6.24; N, 12.38. $[\alpha]_D^{20}$ +4.6 (*c* 0.68). IR: ν_{max} 3414, 3000, 1743, 1660, 1420, 1392, 1169, and 1077. GC–MS: t_R 8.31; *m/z* 226 (M^+, 17), 168 (5.8), 167 (61), 129 (5.1), 128 (66), 125 (12), 113 (12), 112 (5.3), 100 (5.6), 97 (12), 96 (9.4), 70 (5.3), 69 (17), 68 (100), 67 (5.0), 56 (5.1), 55 (16), 44 (6.6), 43 (9.2), 42 (8.6), 40 (6.6), 39 (7.7). ^{1}H NMR (300 MHz, DMSO-d_6): 1.80–2.14 [3H, m, CH_2C*H*H pyrrolidine]; 2.31–2.48 [2H, m, CH_2CH*H* pyrrolidine, CONHCH_2C*H*H]; 2.67 [1H, ddd, CONHCH_2CH*H*, *J*=17.1, 7.8, 3.0]; 3.08 [1H, dq, CONHC*H*HCH_2, *J*=15.3, 5.1]; 3.60 [3H, s, OCH_3]; 3.56–3.68 [1H, m, CONHCH*H*CH_2]; 4.45 [1H, dd, C*H*CO_2Me, *J*=8.7, 3.0]; 4.74 [1H, t, C*H*CONH, *J*=7.6]; 8.05 [1H, br t, N*H*, *J*=5.2]. ^{13}C NMR (75 MHz): 26.3 and 26.5 [2C, *C*H_2 pyrrolidine]; 35.6 [CONH*C*H_2CH_2]; 36.4 [CONHCH_2*C*H_2]; 51.8 [*C*H_3]; 57.2 [*C*HCONHCH_2]; 60.0 [*C*HCH_2O]; 168.8, 170.1 and 171.8 [3C, *C*O].

4.18.3. Compound **64**=**34**

Chromatography with CH_2Cl_2/MeOH 98:2→9:1 gave **64** in 61% overall yield. $[\alpha]_D^{20}$ +37.3 (*c* 0.74, CH_2Cl_2/MeOH 9:1).

4.18.4. Compound **65**=*ent*-**35**

Chromatography with CH_2Cl_2/MeOH 98:2→9:1 gave **64** in 73% overall yield. $[\alpha]_D^{20}$ +28.1 (*c* 0.60, CH_2Cl_2/MeOH 9:1).

Acknowledgements

The authors gratefully thank Mr. Andrea Galatini, Dr. Valeria Rocca, and Dr. Carlo Scapolla for HPLC analysis, MUR (PRIN04 and PRIN06), University of Genova, and Fondazione S. Paolo for financial support.

References and notes

1. Virgilio, A.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11580–11581; Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334–4344; Nouvet, A.; Binard, M.; Lamaty, F.; Martinez, J.; Lazaro, R. *Tetrahedron* **1999**, *55*, 4685–4698; Freidinger, R. M. *J. Med. Chem.* **2003**, *46*, 5553–5566.
2. Banfi, L.; Basso, A.; Damonte, G.; De Pellegrini, F.; Galatini, A.; Guanti, G.; Monfardini, I.; Riva, R.; Scapolla, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1341–1345.
3. Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854.
4. Belvisi, L.; Bernardi, A.; Colombo, M.; Manzoni, L.; Potenza, D.; Scolastico, C.; Giannini, G.; Marcellini, M.; Riccioni, T.; Castorina, M.; LoGiudice, P.; Pisano, C. *Bioorg. Med. Chem.* **2006**, *14*, 169–180.
5. Golebiowski, A.; Jozwik, J.; Klopfenstein, S. R.; Colson, A. O.; Grieb, A. L.; Russell, A. F.; Rastogi, V. L.; Diven, C. F.; Portlock, D. E.; Chen, J. J. *J. Comb. Chem.* **2002**, *4*, 584–590.
6. Belvisi, L.; Caporale, A.; Colombo, M.; Manzoni, L.; Potenza, D.; Scolastico, C.; Castorina, M.; Cati, M.; Giannini, G.; Pisano, C. *Helv. Chim. Acta* **2002**, *85*, 4353–4368.
7. Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley: Weinheim, 2005.
8. Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.
9. Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1–140.
10. Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321–3329.
11. Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.
12. Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2003**, *44*, 7655–7658; Anthoine Dietrich, S.; Banfi, L.; Basso, A.; Damonte, G.; Guanti, G.; Riva, R. *Org. Biomol. Chem.* **2005**, *3*, 97–106; Banfi, L.; Basso, A.; Guanti, G.; Lecinska, P.; Riva, R. *Org. Biomol. Chem.* **2006**, *4*, 4236–4240; Banfi, L.; Basso, A.; Guanti, G.; Paravidino, M.; Riva, R. *QSAR Comb. Sci.* **2006**, *25*, 457–460; Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron* **2006**, *62*, 8830–8837; Banfi, L.; Basso, A.; Guanti, G.; Lecinska, P.; Riva, R.; Rocca, V. *Heterocycles* **2007**, *73*, in press. doi:10.1016/j.tet.2006.02.073; Banfi, L.; Basso, A.; Cerulli, V.; Guanti, G.; Riva, R. submitted for publication.
13. Banfi, L.; Basso, A.; Guanti, G.; Kielland, N.; Repetto, C.; Riva, R. *J. Org. Chem.* **2007**, *72*, 2151–2160.
14. Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2004**, *45*, 6637–6640.
15. Pinnen, F.; Zanotti, G.; Lucente, G. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1311–1316.
16. Gudasheva, T. A.; Vasilevich, N. I.; Ostrovskaja, R. U.; Trofimov, S. S.; Voronina, T. A.; Skoldinov, A. P.; Rosantsev, G. G. *Pharm. Chem. J. (Engl. Transl.)* **1996**, *30*, 562–567.
17. Stöckel-Maschek, A.; Stiebitz, B.; Koelsch, R.; Neubert, K. *Bioorg. Med. Chem.* **2005**, *13*, 4806–4820.
18. Larcheveque, M.; Lalande, J. *Tetrahedron* **1984**, *40*, 1061–1065; Gringore, O. H.; Rouessac, F. P. *Org. Synth.* **1985**, *63*, 121–123.
19. Mulzer, J.; Meier, A.; Buschmann, J.; Luger, P. *Synthesis* **1996**, 123–132; Eguchi, S. *Arkivoc* **2005**, *ii*, 98–119.
20. Pyrroline **13** is quite stable if stored at −25 °C for about one month. A prolonged storage requires indeed a chromatography to remove by-products arising from a partial decomposition.
21. This was proved by NMR analysis of the diastereomeric Mosher's esters of **8**. Later on the racemization was excluded in the whole sequence, including also the Ugi reaction, as reported in Ref. 14.

22. We preferred to isolate **13** and to perform the MCR as a separate step, although recently an efficient one-pot Staudinger/aza-Wittig/Ugi reaction on different sized cyclic imines has been reported (see: (a) Timmer, M. S. M.; Risseeuw, M. D. P.; Verdoes, M.; Filippov, D. V.; Plaisier, J. R.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *Tetrahedron: Asymmetry* **2005**, *16*, 177–185; (b) Bonger, K. M.; Wennekes, T.; de Lavoir, S. V. P.; Esposito, D.; van den Berg, R. J. B. H. N.; Litjens, R. E. J. N.; van der Marel, G. A.; Overkleeft, H. S. *QSAR Comb. Sci.* **2006**, *25*, 491–503).
23. This isocyanide can also be conveniently prepared with higher degree of purity with respect to the commercial product through a two-step sequence, transforming *p*-anisidine into the corresponding formamide (HCO_2H, DMF, CH_2Cl_2, rt, 95%) and submitting this intermediate to the usual dehydration procedure ($POCl_3$, Et_3N, CH_2Cl_2, −30 °C→0 °C, 87%).
24. Lindhorst, T.; Bock, H.; Ugi, I. *Tetrahedron* **1999**, *55*, 7411–7420.
25. Linderman, R. J.; Binet, S.; Petrich, S. R. *J. Org. Chem.* **1999**, *64*, 336–337.
26. Concerning the preparation of Linderman's isocyanide we improved the literature procedure, submitting the formamide precursor to dehydration with diphosgene, *N*-methylmorpholine, CH_2Cl_2, 0 °C (88% yield).
27. Zhang, L.; Kauffman, G. S.; Pesti, J. A.; Yin, J. *J. Org. Chem.* **1997**, *62*, 6918–6920; Rew, Y.; Goodman, M. *J. Org. Chem.* **2002**, *67*, 8820–8826.
28. Actually, these lactones shown to be not very stable in the presence of nucleophiles such as alcohols. For example, when purified by chromatography with an eluent containing methanol, a partial conversion into the open methyl ester was observed.
29. Jones method worked well, but work-up was crucial and required to substitute $NaHSO_3$, as reducing agent, with a little amount of methanol: otherwise the following hydrogenolysis did not occur.
30. Belyaev, A. A. *Tetrahedron Lett.* **1995**, *36*, 439–440.
31. Szardenings, A. K.; Burkoth, T. S.; Lu, H. H.; Tien, D. W.; Campbell, D. A. *Tetrahedron* **1997**, *53*, 6573–6593; Hulme, C.; Morrissette, M. M.; Volz, F. A.; Burns, C. J. *Tetrahedron Lett.* **1998**, *39*, 1113–1116; Hulme, C.; Peng, J.; Louridas, B.; Menard, P.; Krolikowski, P.; Kumar, N. V. *Tetrahedron Lett.* **1998**, *39*, 8047–8050; Szardenings, A. K.; Antonenko, V.; Campbell, D. A.; DeFrancisco, N.; Ida, S.; Shi, L.; Sharkov, N.; Tien, D.; Wang, Y.; Navre, M. *J. Med. Chem.* **1999**, *42*, 1348–1357; Marcaccini, S.; Pepino, R.; Cruz Pozo, M. *Tetrahedron Lett.* **2001**, *42*, 2727–2728; Dinsmore, C. J.; Beshore, D. C. *Tetrahedron* **2002**, *58*, 3297–3312; Cho, S.; Keum, G.; Kang, S. B.; Han, S.-Y.; Kim, Y. *Mol. Divers.* **2003**, *6*, 283–286; Sollis, S. L. *J. Org. Chem.* **2005**, *70*, 4735–4740; Wyatt, P. G.; Allen, M. J.; Borthwick, A. D.; Davies, D. E.; Exall, A. M.; Hatley, R. J. D.; Irving, W. R.; Livermore, D. G.; Miller, N. D.; Nerozzi, F.; Sollis, S. L.; Szardenings, A. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2579–2582; Habashita, H.; Kokubo, M.; Hamano, S.; Hamanaka, N.; Toda, M.; Shibayama, S.; Tada, H.; Sagawa, K.; Fukushima, D.; Maeda, K.; Mitsuya, H. *J. Med. Chem.* **2006**, *49*, 4140–4152; Lin, Q.; Blackwell, H. E. *Chem. Commun.* **2006**, 2884–2886.
32. Hulme, C.; Peng, J.; Morton, G.; Salvino, J. M.; Herpin, T.; Labaudiniere, R. *Tetrahedron Lett.* **1998**, *39*, 7227–7230.
33. Kennedy, A. L.; Fryer, A. M.; Josey, J. A. *Org. Lett.* **2002**, *4*, 1167–1170.
34. Mori, K.; Rikimaru, K.; Kan, T.; Fukuyama, T. *Org. Lett.* **2004**, *6*, 3095–3097; Rikimaru, K.; Yanagisawa, A.; Kan, T.; Fukuyama, T. *Synlett* **2004**, 41–44; Rikimaru, K.; Mori, K.; Kan, T.; Fukuyama, T. *Chem. Commun.* **2005**, 394–396.
35. The procedure was first optimized on a compound similar to the one described in Ref. 24 (only $^{n}BuNH_2$ was used instead of $MeNH_2$ as amine input to prepare it through the Ugi reaction) varying: (a) the base (^{t}BuOK, KHMDS, DBU, NaH, MeONa; (b) the temperature; (c) the work-up conditions (quenching with NH_4Cl, HCl, citric acid); (d) the terminal group of the carbonate (Me, ^{i}Bu, ^{t}Bu). No improvement was noticed when *iso*-butyl carbonate was used. When *tert*-butyl carbonate was employed always a mixture of products was obtained, the major one being the primary alcohol, followed by the acyl oxazolidinone and, finally, by the desired methyl ester.
36. Under the same conditions model compound of Ref. 35 gave exclusively the desired methyl ester.
37. Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233–4236.
38. Mjalli, A. M. M.; Sarshar, S.; Baiga, T. J. *Tetrahedron Lett.* **1996**, *37*, 2943–2946.
39. Racemization did not occur during the preparation of the isocyanide, provided that dehydration of its precursor (the formamide) is performed with diphosgene and not with $POCl_3$. The stereochemical problem lies exclusively in the Ugi MCR, since we demonstrated that in the corresponding Passerini reaction, employing the same components but in the absence of the primary amine, no racemization occurred, as expected ((a) See Ref. 9; (b) Semple, J. E.; Owens, T. D.; Nguyen, K.; Levy, O. E. *Org. Lett.* **2000**, *2*, 2769–2772; (c) Owens, T. D.; Araldi, G.-A.; Nutt, R. F.; Semple, J. E. *Tetrahedron Lett.* **2001**, *42*, 6271–6274; (d) Basso, A.; Banfi, L.; Riva, R.; Piaggio, P.; Guanti, G. *Tetrahedron Lett.* **2003**, *44*, 2367–2370).
40. Xia, Q.; Ganem, B. *Org. Lett.* **2002**, *4*, 1631–1634; Wang, Q.; Xia, Q.; Ganem, B. *Tetrahedron Lett.* **2003**, *44*, 6825–6827; Fayol, A.; Zhu, J. *Org. Lett.* **2004**, *6*, 115–118; Cuny, G.; Gámez Montaño, R.; Zhu, J. *Tetrahedron* **2004**, *60*, 4879–4885; Fayol, A.; Housseman, C.; Sun, X. W.; Janvier, P.; Bienaymé, H.; Zhu, J. *Synthesis* **2005**, 161–165; Fayol, A.; Zhu, J. *Org. Lett.* **2005**, *7*, 239–242; Tron, G. C.; Zhu, J. *Synlett* **2005**, 532–534.
41. Basso, A.; Banfi, L.; Guanti, G.; Riva, R.; Riu, A. *Tetrahedron Lett.* **2004**, *45*, 6109–6111.