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Synthetic studies on *Stemona* alkaloids. Construction of the sessilifoliamides B and C and 1,12-secostenine skeleton

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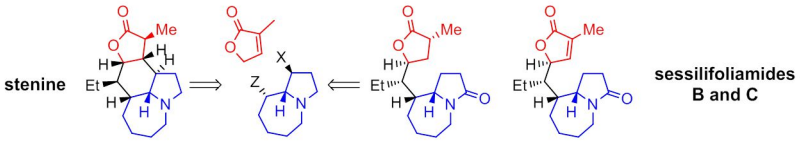

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Synthetic studies on *Stemona* alkaloids. Construction of the sessilifoliamides B and C and 1,12-secostenine skeleton

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ABSTRACT

An original synthetic approach to the *Stemona* alkaloids stenine and sessilifoliamides B and C has been explored. The strategy relays on the early construction of the pyrroloazepine core (rings A and B) and posterior addition of the furanone (ring D) and ethyl chain at C-10, which are the common structural features of the three alkaloids. The formation of the azabicyclic nucleus through an intramolecular Morita-Baylis-Hillman reaction of a properly substituted pyrrolidone has been extensively investigated by modifications on the substrate and all the parameters involved in the process and an efficient protocol in terms of yield and stereoselectivity has been developed. Despite many alternative tactics were explored, insuperable difficulties found in the last synthetic steps have frustrated the completion of the syntheses. However, along the way, a plethora of new compounds was prepared, some of them containing the full skeleton of the targeted alkaloids, which can be useful for future synthetic applications.

1. Introduction

The development of new medicinal drugs has often found its inspiration in the curative properties of some plants used in traditional folk medicine and, hence, the isolation and characterization of the bioactive principles of these plants and, ultimately, their total synthesis have been (and still are) major challenges for organic chemists. The *Stemona* alkaloids form a group of significant constituents of the extracts of several plants of the *Stemonaceae* family (*Stemona, Croomia* and *Stichoneuron* genera) that have been used for years in eastern Asian countries for the treatment of respiratory disorders and parasitic diseases like helminthiasis and also as domestic insecticides.[1] At present, more than 180 *Stemona* alkaloids have been described,[2] but the discovery of new members of this family is continuously reported in the literature. All the *Stemona* alkaloids are polycyclic and the majority present a pyrrolo- (more frequently) or pyrido[1,2-*a*]azepine core as the common structural feature. They also incorporate at least one α-methyl-γ-butyrolactone substructure linked to the azabicyclic nucleus in a spiro or fused mode or as a substituent.[3] On the basis of their chemical structure, the *Stemona* alkaloids were initially classified by Pilli into six groups,[3a] which were later extended to eight with the discovery of new members of the family (Figure 1, A); six of these groups display the pyrroloazepine nucleus, one contains the pyridoazepine core and a miscellaneous group does not present any of these motifs.[3b] Considering their biogenetic connections, Greger suggested an alternative classification in three skeletal types, which differ on the carbon chain attached to C-9 of the pyrroloazepine core (Figure 1, B).[1c] More recently, combining both criteria, a third classification has been proposed into two classes (hemiterpenoid pyrrolidine and monoterpenoid pyrrolidine) and fourteen types.[2]

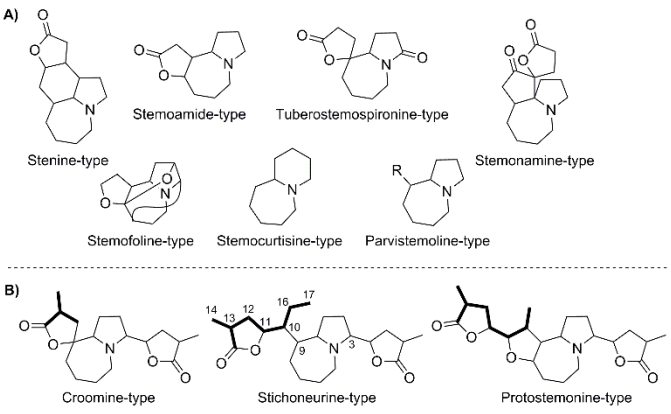
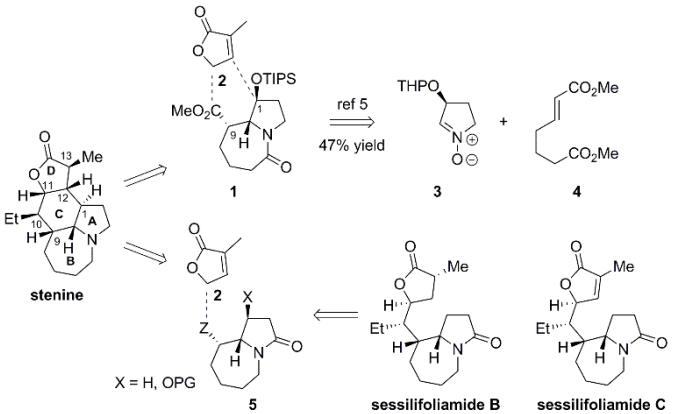


Figure 1. Classification of *Stemona* alkaloids based on: A) their chemical structure; B) their biogenetic connections

The challenging molecular architectures of the *Stemona* alkaloids have motivated the development of profuse synthetic investigations,[3,4] but the total syntheses reported to date are limited

to a relatively small number of such compounds. Some years ago, we designed a synthetic strategy, which relied on the use of chiral cyclic nitrones as templates for the stereoselective construction of the pyrroloazepine core and pursued the preparation of intermediates common to several *Stemona* alkaloids.[5] This approach was successfully applied in completing enantioselective syntheses of the putative structure of stemonidine, stemospironine and several other analogs, all of them belonging to the tuberostemonine-type according to Pilli's classification.[6] To investigate the applicability of the same strategy for the synthesis of alkaloids of the stenine group, the key azabicycle **1** (Scheme 1) was prepared from nitrone **3** and diester **4** in six steps and 47% overall yield.[5] In our retrosynthetic analysis of stenine, the silyl ether and ester group, respectively attached to positions C-1 and C-9 of **1**,[7] were intended to be handled for connecting lactone **2** (ring D) and subsequently closing the six member ring C. A strategy based on the initial assemblage of rings A and B has not been reported in any previous synthesis of stenine.[8] However, the fact that sessilifoliamides B and C present the same connectivity as stenine, except for lacking the C-1/C-12 bond, suggests a biogenetic connection as it was proposed by Greger, who enclosed these three alkaloids in the same stichoneurine-type group. Hence, the connection of C-1 and C-12 from a tricyclic precursor with the sessilifoliamides B/C skeleton with concomitant formation of ring C at the end of the synthetic sequence would be a biogenetically inspired approach to stenine that we judged worthy to explore. In contrast to sessilifoliamides B and C, wherein ring A is a pyrrolidone, in the azabicycle **1** the protecting carbonyl group of the nitrogen atom is located in the seven member ring B, therefore we decided to examine also a parallel route through an analogous intermediate **5**, wherein position 1 may be unsubstituted (X= H) or bear a protected hydroxyl group (X=OPG) and which would provide a more straightforward access to the sessilifoliamides. To the best of our knowledge, only one synthesis of (–)-sessilifoliamide C and none of sessilifoliamide B have been reported to date.[9] Considering that the relative configuration assigned by chemical correlation to sessilifoliamide C[10] is at C-10 and C-11 opposite to that of stenine, it was interesting to prepare diverse diastereoisomeric analogs for the synthetic studies.

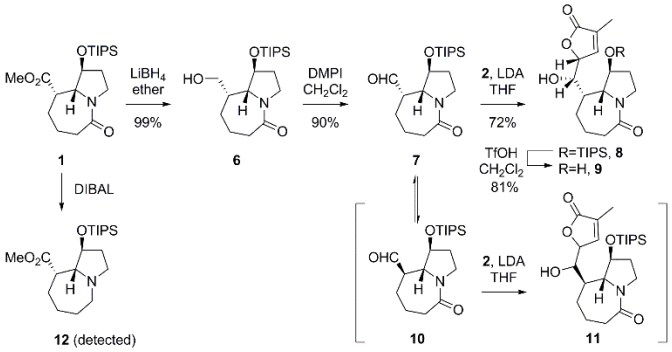


Scheme 1. Retrosynthetic analysis of stenine and sessilifoliamides B and C.

2. Results and discussion

2.1. Synthetic studies from the key intermediate 1

Our first efforts were directed to the installation of the lactone ring D through manipulation of the ester group in **1** by using aldol-type chemistry. Not surprisingly, the attempted vinylogous Claisen reaction between ester **1** and lactone **2** was unsuccessful and it was necessary to activate the electrophile by preparing the corresponding aldehyde **7** (Scheme 2). The ester group of **1** was reluctant to react with DIBAL-H and, after persistent treatment, amine **12** was the exclusive product detected. Alternatively, reduction of **1** to alcohol **6** with $LiBH_4$, followed by Dess-Martin oxidation provided aldehyde **7**, which was immediately processed to the next step in view of its limited stability, being prone to epimerize to **10**. The vinylogous aldol addition was accomplished in 72% yield by direct reaction[11] between the lithium dienolate of **2** and aldehyde **7** in THF at –78 °C and was completely stereoselective, furnishing the adduct **8**, which configuration was unambiguously established by X-ray analysis of the corresponding alcohol **9** (Figure 2). The Mukayama aldol methodology, frequently employed for vinylogous addition of 2(5*H*)-furanones to aldehydes,[12] when using the TIPS derivative of **2**, proved ineffective for **7**, most probably because of the higher steric demand of the dienoxysilane nucleophile compared to the lithium dienolate. Indeed, the carbonyl group in **7**, located in the concave face of the azabicycle, must be hardly accessible to external reagents, as it is the case of the ester group in **1**, which proved reluctant to react with the bulky DIBAL-H. Eventually, if the starting aldehyde **7** was contaminated with its epimer **10**, a second isomer **11** was also present in the vinylogous aldol crude product that could be even isolated, but its relative configuration at the new stereogenic center was not determined.



Scheme 2. Preparation of tricyclic intermediate **9**.

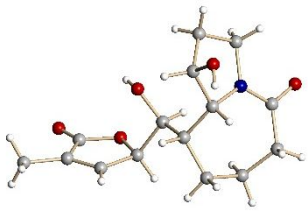
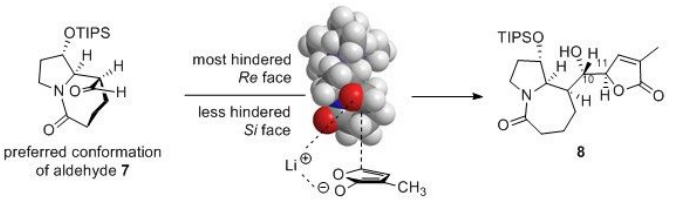


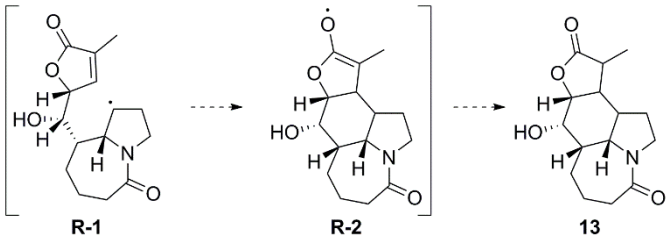
Figure 2. X-Ray structure of alcohol **9**.

The complete diastereoselectivity observed in the addition of the lithium enolate of lactone **2** to aldehyde **7** may be rationalized by the hypothetical transition state depicted in Scheme 3. According to a simple tridimensional molecular model, in the preferred conformation of aldehyde **7** the *Si* face is more accessible to the approach of an external nucleophile, leading to the *S* configuration at C-10. On the other hand, the *R* configuration at C-11 is consistent with an enolate orientation in which the lithium cation is coordinated with the carbonyl oxygen and the bulky methyl group is pointing away from the aldehyde.



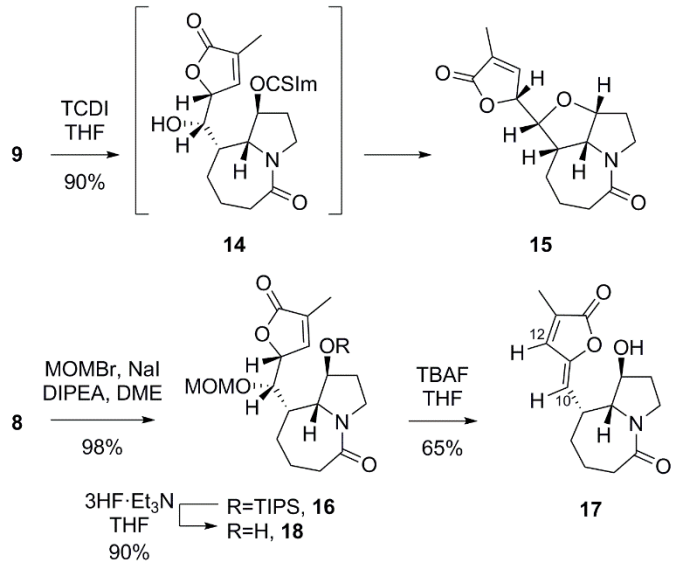
Scheme 3. Molecular model of aldehyde **7** (ChemBioDraw Ultra 14.0) and hypothetical transition state for the addition of the lithium enolate of lactone **2**.

With alcohol **9** in hands, our next endeavor was to generate a radical at C-1, **R-1**, that was expected to induce a 6-exo-trig cyclization to form the C ring of stenine (Scheme 4). The formation of six member rings by intramolecular insertion of a radical into a carbon-carbon double bond has been broadly illustrated,[13] including the participation of a 2(5*H*)-furanone subunit acting as the radical acceptor through the β-position.[14] In the case under study, we expected the conversion of **R-1** to a more stable enoxy radical **R-2**, which after hydrogen abstraction would provide a product **13** with the tetracyclic structure of stenine.



Scheme 4. Expected evolution of a radical generated at C-1.

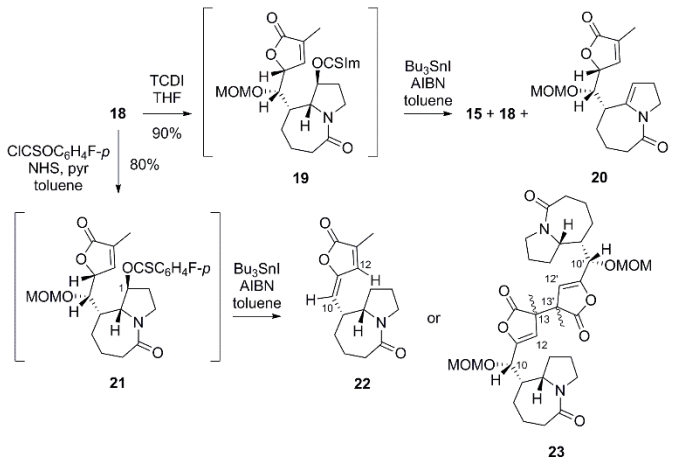
Thiocarbamates are among the derivatives most frequently used for the generation of free radical intermediates.[15] Treatment of diol **9** with TCDI in THF at room temperature provided thiocarbamate **14** (Scheme 5). As anticipated, the sterically hindered hydroxyl group at C-10 was unreactive under these conditions and **14** could be isolated in 90% yield, but, unfortunately, the thiocarbamate spontaneously cyclized to the ether **15**, even keeping it at 4 °C under inert atmosphere. Hence, we decided to orthogonally protect



Scheme 5. Preparation of the MOM derivative **18**.

the alcohol **8**, prior to the preparation of the radical precursor. After several failed attempts of benzylation, we succeeded in preparing the methoxymethyl derivative **16** by heating a mixture of **8**, MOMBr, NaI, and DIPEA in refluxing DME.[16] The desilylation of **16** was initially assayed by treatment with TBAF in THF, but this reaction furnished alkene **17** in 65% yield, as the only isolable product. The *Z* configuration of **17** was evidenced by a strong NOE interaction between the olefinic protons at C-10 and C-12. This stereochemistry is in agreement with an E1cB mechanism, namely previous formation of the dienolate followed by elimination of the MOMO fragment, and not consistent with a concerted E2 process that would lead to the *E* isomer. The competitive elimination reaction could be avoided by performing the desilylation by treatment of **16** with a large excess of the complex $3HF \cdot Et_3N$,[17] and the alcohol **18** was isolated in 90% yield.

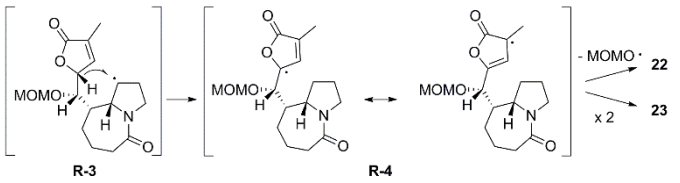
Next, alcohol **18** was converted into the corresponding imidazolylthiocarbamate **19**, which was highly sensitive to any trace of acid and was rapidly treated with Bu_3SnH and AIBN in refluxing toluene in order to generate the radical species (Scheme 6). This reaction was attempted many times under different conditions, changing the relative amounts of Bu_3SnH and AIBN and their rate of addition to the refluxing solution of the substrate. In all the different runs we always observed partial hydrolysis of the carbamate, reverting to alcohol **18**, along with the formation of the cyclic ether **15** and a new compound identified as the enamide **20**. Since these three products were detected irrespective of the quantities of reagents added, we suspected that they may have been generated by thermal activation of the substrate without any intermediacy of a radical. To confirm or discard this hypothesis, in a reference experiment, thiocarbamate **19** alone was heated in refluxing toluene for 12 hours and we observed that the alcohol **18** and the ether **15** were indeed formed, but the enamide **20** was not detected and hence it should be produced by evolution of an intermediate radical species. In any case, the competitive thermal reactions predominated and invalidated the reaction for synthetic purposes. As an alternative, the more resistant-to-hydrolysis *p*-fluorophenylthiocarbamate **21** was prepared[18] and the radical reaction was attempted from this new derivative under two different conditions. In a first experiment, a 0.07M solution of **21** in toluene was added to a refluxing solution of Bu_3SnH (4 eq) and AIBN (1 eq) in the same volume of toluene and the mixture was heated under reflux for three hours. These conditions, usually applied for the Barton-McCombie deoxygenation reaction,[15a] were particularly intended to ensure the formation of the radical from **21**. After purification of the crude material, we were able to identify only one product that was characterized as the alkene **22**, to which we assigned the *E* configuration due to the lack of NOE



Scheme 6. Attempted radical cyclization from **18**.

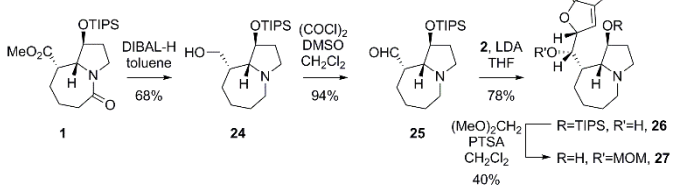
between H-10 (δ 5.14) and H-12 (δ 6.97). In a second experiment, a 0.025M solution of **21** in toluene and another solution of Bu_3SnH (4 eq) and AIBN (1 eq) in the same volume of toluene were simultaneously added, during a 12 h period, over the same volume of refluxing toluene and then heating was prolonged for two additional hours. From this trial we isolated a fraction containing three stereoisomers of the dimeric structure **23**. The ^1H NMR spectrum of the mixture of **23** is consistent with two minor isomers with axial symmetry (*R,R* and *S,S* in the new stereogenic centers at C-13/13'), each one presenting one set of signals (δ 5.76 and 5.75 for H-12 and δ 4.73 and 4.65 for H-10, respectively), and one asymmetric major isomer (*R,S* at C-13/13'), presenting two sets of signals with identical relative area (δ 5.50 and 5.37 for H-12 and δ 4.33 and 4.26 for H-10).

The formation of **22** and **23** can be only explained by the intermediacy of radical species (Scheme 7). Hypothetically, from the originally formed radical **R-3**, hydrogen atom abstraction of the allylic position is preferred over 6-exo-trig cyclization. The new radical formed **R-4** may then evolve by losing the MOMO group and leading to diene **22** or by dimerizing to **23**. Curiously enough, the dimerization was only observed when the reaction was performed under higher dilution, but, in any case, it was clear that the generated radical did not have the proper geometry to cyclize and, hence, the planned synthetic route to stenine was invalidated.



Scheme 7. Evolution of the intermediate radical **R-3** to the isolated products.

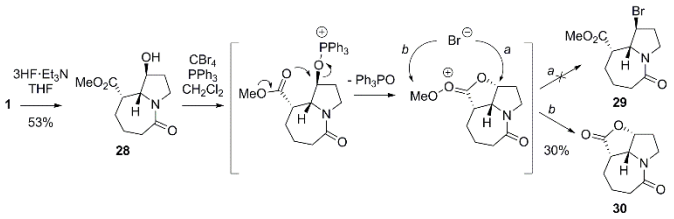
We reasoned that a change in the nitrogen atom hybridization from sp^2 to sp^3 would provide a more flexible radical and hopefully facilitate the desired cyclization. Since the selective reduction of lactam **16** to the corresponding tertiary amine[19] met with failure, we decided to perform the reduction in an earlier step of the sequence (Scheme 8). After extensive experimentation, the aminoalcohol **24** could be prepared in an acceptable yield by treatment of lactam **1** with an excess of DIBAL-H in toluene.[20] The subsequent Swern oxidation[21] delivered the aminoaldehyde **25**, which was rapidly reacted with the lithium enolate of furanone **2**, furnishing the addition product **26** as a single isomer. Although the relative configuration of **26** could not be firmly established, we assumed that it was the same as in the analogous lactam **9**. Then, by analogy with the precedent investigations within the lactam series of intermediates, the protection of the hydroxyl group of **26** as the MOM ether was intended. Unfortunately, the above conditions that had worked very well for the derivatization of lactam **9**, when applied to amine **26**, led to a complex mixture of decomposition products. An alternative protocol, using



Scheme 8. Truncated sequence with intermediate amines.

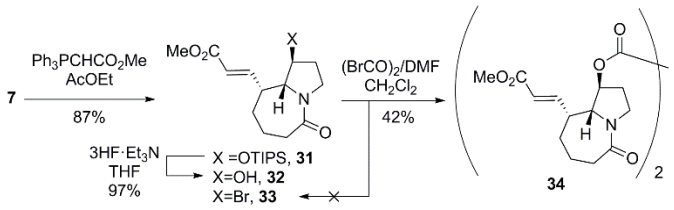
dimethoxymethane and *p*-toluensulfonic acid in CH_2Cl_2,[22] produced simultaneous desilylation, giving the MOM ether **27**, as the only product, which was isolated in 40% yield and presented low stability, disabling any purpose of going further in the synthetic sequence.

In view that the vinylogous aldol addition of lactone **2** had worked well on both lactam **7** and amine **25**, we next considered the possibility of linking the lactone ring D to position 1 of the azabicycle through a metal mediated carbon-carbon coupling methodology in the first place, and then generating ring C through the aldol type process. To explore this option, we intended to replace the OTIPS substituent in lactam **1** by a bromine atom (Scheme 9). With this purpose, the TIPS group was removed and the resulting alcohol **28** was treated with CBr_4 and Ph_3P in CH_2Cl_2.[23] We predicted that the substitution reaction would take place with retention of configuration at C-1 thanks to the anchimeric assistance of the ester group (path *a*); however, instead of the expected bromine **29**, this reaction delivered lactone **30**, as the unique identifiable product, most probably because the competitive attack of the bromide to the methyl group (path *b*) was favored.



Scheme 9. Attempted preparation of bromide **29**.

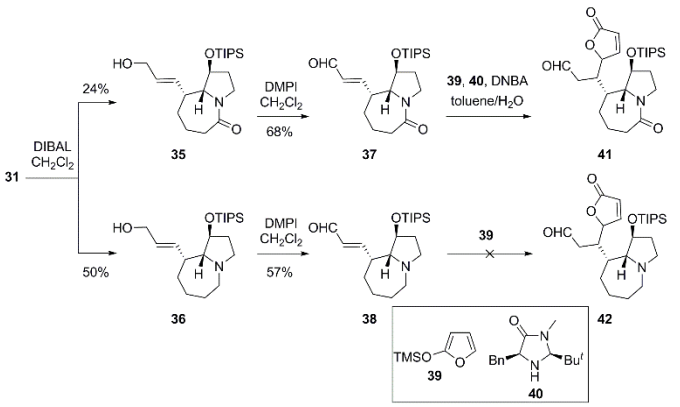
As a mean to overcome this problem, we decided to prepare the homologous ester **32**, which keeps the electrophilic character at C-10, enabling conjugate addition of the lactone moiety, incorporates the two-carbon fragment (C-12/C-13) present in the target alkaloids, and disables the formation of undesired products as **15** or **30** by oxycyclization (Scheme 10). The Wittig alkenylation of aldehyde **7** in refluxing ethyl acetate as the solvent furnished the expected ester **31** in high yield with excellent stereoselectivity, which was desilylated to the corresponding alcohol **32**. However, several attempts to convert **32** into the corresponding bromide **33**, including treatment with CBr_4/Ph_3P, SOBr,[24] or $(COBr)_2$/DMF,[25] met with failure, being the bisoxalate **34** the only isolated product under the last conditions.



Scheme 10. Preparation of ester **31** and attempted conversion to bromide **33**.

In any case, we decided to test the viability of installing the lactone ring D by means of a conjugate addition reaction. To this aim, we intended to adapt to our substrates the conditions described by McMillan and coworkers for the enantioselective Mukaiyama-Michael reaction between silyloxyfurans and simple α,β-unsaturated aldehydes.[26] Hence, it was necessary to activate the electrophile by reduction of the α,β-unsaturated ester **31** to the

corresponding aldehyde (Scheme 11). In the event, treatment of **31** with DIBAL-H (4 eq) in CH_2Cl_2 at –78 ºC led to a mixture of the expected hydroxylactam **35** and the hydroxylamine **36** in a 1:2 ratio and 74% overall yield. Other reducing agents ($LiBH_4$, $LiAlH_4$) and/or conditions gave lower yields and significant amounts of decomposition products. Lactam **35** and amine **36** were then converted into the corresponding aldehydes **37** and **38** by oxidation with the Dess-Martin periodinane (DMPI). Unfortunately, despite many efforts were made by exploring different silyloxyfuranes, organocatalytic bases, additives, solvents and conditions, only in one case we were able to detect the expected addition product, when the reaction between lactam **37** and silyloxyfurane **39** was performed in the presence of the imidazolidinone **40**, 2,4-dinitrobenzoic acid (DNBA) and water, in toluene. Under these conditions, in a fraction of the crude product, compound **41** was recognized as a mixture of three diastereoisomers in an overall yield around 15%.

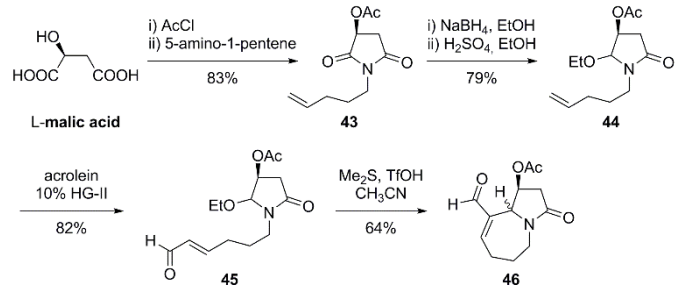


Scheme 11. Synthesis of aldehydes **37** and **38** and attempted conjugate addition of silyloxyfurane **39**.

In view of these unsatisfactory results, we next focused our investigations on exploring the alternative route through a pyrrolidone intermediate **5** (Scheme 1), which would be straightforwardly related to the sessilifoliamide B/C structure.

2.2. Synthetic atudies based on the key synthon 5

In a publication describing the synthesis of grandisine D, as part of a supplementary study, Tamura and coworkers reported the preparation of aldehyde **46** starting from L-malic acid and using an intramolecular Morita-Baylis-Hillman (MBH) reaction of a properly substituted pyrrolidone **45** to generate the azepine ring (Scheme 12).[27] The synthesis involved four steps, the overall yield was 34%, and the bicyclic lactam was obtained as a roughly 2:1 (*trans*/*cis*) mixture of diastereoisomers, which could not be chromatographically separated.



Scheme 12. Synthesis of aldehyde **46** described by Tamura and coworkers.[27]

The similarity between aldehyde **46** and our key synthon **5** encouraged us to explore the possibility of adapting the reported synthesis of **46** to a suitable intermediate for the targeted alkaloids. In our laboratories, the preparation of imide **43** could be slightly improved to 86% yield by treating 2-acetoxy-L-malic anhydride with 5-amino-1-pentene generated in situ from the corresponding hydrochloride prepared by a Gabriel synthesis,[28] the subsequent reduction to the acylaminal **44** could be accomplished in 93% yield, and the cross metathesis with acrolein and 5% of the second generation Hoveyda-Grubbs catalyst (HG-II) in CH_2Cl_2 was achieved in 94% yield. Then, the MBH cyclization was studied in detail with the aim of finding conditions to improve the efficiency and stereoselectivity of the process. Originally, this transformation was described to proceed by using triflic acid (to generate the iminium ion) and dimethyl sulfide (as the nucleophile to make the enolate) in acetonitrile as the solvent.

Based on the published studies leading to the formation of the indolizidine intermediate for grandisine D, we expected that eventual improvements on yield and/or diastereoselectivity in the cyclization to the pyrroloazepine system of interest would be mainly associated to modification of the acid promoter and, hence, the MBH reaction was assayed in the presence of various Lewis acids (Table 1). Firstly, we intended to reproduce the reported conditions (entry 1), which in our hands lead to an even lower *trans/cis* ratio of **46**. Boron trifluoride (entry 2) gave lower conversion and stereoselectivity, while trimethylsilyl triflate (entry 3), dibutylboryl triflate (entry 4) and triisopropylsilyl triflate (entry 5) gave all better conversion but low diastereoselectivity, and changing the solvent to ether (entries 6-7) did not produce significant improvements either. The most interesting observation of this study was that the substitution of TfOH by TMSOTf improved the yield of isolated **46** from 64% to 82% without decreasing the diastereoselectivity. In summary, the overall yield of the sequence from L-malic acid to the azabicyclic acetate **46** was enhanced from the reported 34% to 62%.

Table 1. Synthesis of aldehydes **37** and **38** and attempted conjugate addition of silyloxyfurane **39**.[a]

Entry	Acid Promoter	Solvent	Conversion[b]	trans/cis[b]
1[c]	TfOH	CH_3CN	70%	1.4:1
2	$BF_3{\cdot}Et_2O$	CH_3CN	60%	1.2:1
3	TMSOTf	CH_3CN	100%[d]	2:1
4	Bu_2BOTf	CH_3CN	80%	1:1.1
5	TIPSOTf	CH_3CN	86%	1:1
6	TMSOTf	Et_2O	70%	2:1
7	Bu_2BOTf	Et_2O	90%	2:1

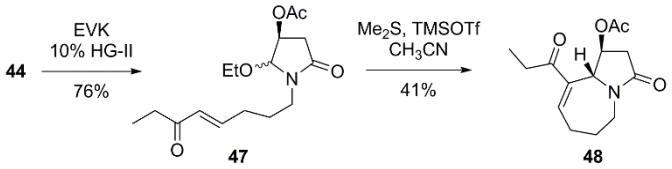
[a]All the reactions were performed using Me_2S as the nucleophile, from –35 ºC to room temperature, for an overall time of 3 h.

[b]Determined by ^1H NMR analysis of the crude material.

[c]Reaction performed under the conditions described in ref. 26.

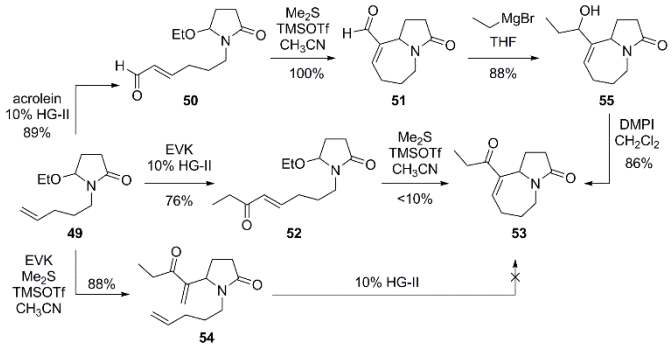
[d]Isolated yield: 82%.

We then explored the possibility of applying an analogous sequence to the preparation of the azabicyclic enone **48**, which contains the C-10 ethyl chain present in the targeted alkaloids (Scheme 13). Unfortunately, both reactions involved in the transformation of acylaminal **44** to enone **48**, the cross metathesis with ethyl vinyl ketone (EVK) and the subsequent intramolecular MBH reaction, gave substantially lower yields compared to the aldehyde analogs, but the bicyclic enone **48** was isolated as a single diastereoisomer, to which we assigned the *trans* relative configuration by comparison of its ^{1}H NMR spectrum with those described for *cis*- and *trans*-**46**.[27]



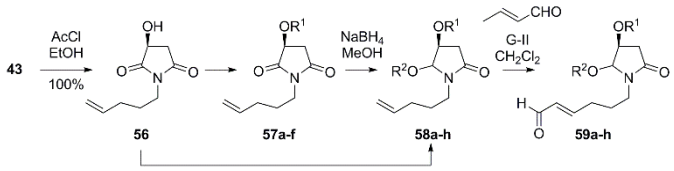
Scheme 13. Preparation of azabicyclic enone **48**.

With the aim of studying the subsequent steps of the synthetic plan on simpler intermediates, we also decided to prepare enal **51** and enone **53** lacking the substituent at C-1 (Scheme 14). Thus, the known acylaminal **49**[29] was converted into **51** by cross metathesis with acrolein followed by MBH cyclization in 89% yield for the two steps. A parallel protocol with EVK as the metathesis partner led to the lineal enone **52** in 76% yield, but its cyclization was very ineffective. We assayed to invert the order of steps and performed an intermolecular MBH reaction between **49** and EVK, which delivered dienone **54** in 88% yield, but the subsequent intramolecular cross metathesis met with failure, leading to polymeric material, despite the reaction was intended under high dilution conditions. Finally, enone **53** was obtained in good yield by ethylmagnesium bromide addition to aldehyde **51** and oxidation with DMPI of the corresponding mixture of diastereoisomeric alcohols **55**.



Scheme 14. Preparation of the model azabicyclic enal **51** and enone **53**.

Next, in the search for a more effective asymmetric induction in the MBH cyclization within the homochiral series of intermediates, we decided to explore the replacement of the acetate substituent in **45** by other hydroxyl derivatives. To this aim, starting from **43**, we synthesized the series of analogs **59** according to the sequence depicted in Scheme 15 (Table 2). Ethanolysis of acetate **43** furnished the free alcohol **56**,[30] from which the benzyl (R^1=Bn), *p*-methoxybenzyl (R^1=PMB), pivaloyl (R^1=Piv), benzoyl (R^1=Bz), *tert*-butyldimethylsilyl (R^1=TBS), and *tert*-butyldiphenylsilyl (R^1=TBDPS) derivatives, **57a-f**, were prepared by standard procedures in good yields. Then, these compounds were reduced to the corresponding acylaminals **58a-f** by treatment with $NaBH_4$ in methanol at –20 ºC. This reduction was totally regioselective except for the TBDPS derivative **57f**, from which a minor amount of the other regioisomer was also identified.[31] On the other hand, **58a**, **58b** and **58f** were obtained as mixtures of two epimers, while for the rest of compounds **58** only one epimer was detected, but it should be noticed that the occurrence of epimers at the aminal position is synthetically inconsequent. On the TBDPS derivative **57f**, the reduction of the imide was assayed in other solvents (EtOH, MeOH/CH_2Cl_2) and with other reducing agents ($LiBH_4$, L-selectride®, $LiEt_3BH$, DIBAL-H, BH_3·THF, and $NaB(OAc)_3H$), but the isolated yields of acylaminal were lower in all cases and the regioselectivity could not be improved either. Two additional acylaminals **58g** and **58h** were prepared by imide reduction of the free alcohol **56** and posterior *in situ* treatment with ethanol or acetone, respectively, under acid catalysis.



Scheme 15. Synthesis of the pyrroloazepinones **59**.

Next, the optimal conditions for the cross metathesis reaction were investigated using **58f** as the model substrate, and it was found that the reaction with crotonaldehyde (easier to handle than acrolein) with 2% molar second generation Grubbs catalyst (G-II) in CH_2Cl_2 at room temperature proceeded quantitatively. The same conditions were then applied to the rest of acylaminals and the enals **59a-h** were all isolated in excellent yields.

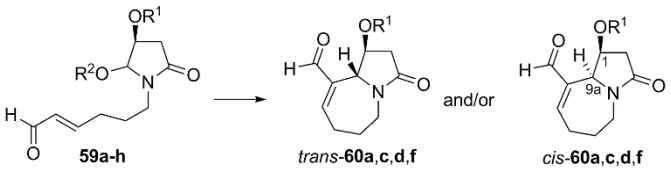
Table 2. Isolated yields of compounds **57a-f**, **58a-h**, and **59a-h**.

Entry	R^1	R^2	**57** (Yield)	**58** (Yield)	**59** (Yield)
1	Bn	H	**57a** (97%)	**58a** (85%)	**59a** (87%)
2	PMB	H	**57b** (92%)	**58b** (61%)	**59b** (89%)
3	Piv	H	**57c** (80%)	**58c** (72%)	**59c** (86%)
4	Bz	H	**57d** (86%)	**58d** (78%)	**59d** (83%)
5	TBS	H	**57e** (92%)	**58e** (61%)	**59e** (86%)
6	TBDPS	H	**57f** (90%)	**58f** (67%) [a]	**59f** (100%)
7	H	Et		**58g** (88%)	**59g** (91%)
8	Me_2C			**58h** (51%)	**59h** (82%)

[a]A regioisomer was also isolated in 11% yield.

With derivatives **59a-h** in hand, we undertook the study of their MBH cyclization (Scheme 16). We hypothesized that the lower regioselectivity observed for the reduction of **57f** compared to the rest of analogs was due to the larger steric hindrance triggered by the bulky TBDPS group, a factor that could now benefit the *trans* stereoselectivity of the cyclization process and, hence, we initially focused the study on this substrate (Table 3). All the reactions were performed at the same temperature (from –35 ºC to room temperature) for a total time of 4 h and the substrate conversion and diastereoisomeric ratio were monitored by ^{1}H NMR analysis of the crude reaction product. The first experiments were done

with TMSOTf as the acid promoter, which had given the best result in the previous cyclization of acetate **45**, and dimethyl sulfide (DMS) as the nucleophile. With this pair of reagents, the reaction in acetonitrile (entry 1) proceeded faster and with higher diastereoselectivity than in CH_2Cl_2 (entry 2). The replacement of DMS by DABCO (entry 3) was ineffective, leaving the substrate unchanged. Then, other acids were tested keeping DMS as the nucleophile and acetonitrile as the solvent. Using $BF_3{\cdot}OEt_2$ (entry 4) the conversion was good but the stereoselectivity very poor, indium triflate (entry 5) did not promote any reaction, and triflic acid (entry 6) did not improve the selectivity. However, triethylsilyl triflate (entry 7) led to total conversion with complete steric induction and, quite surprisingly, afforded exclusively the *cis* isomer **60f** in 68% isolated yield. It is worth mention that, if isolated as a unique product in a fair yield, any diastereoisomer *cis* or *trans* was equally valuable for our synthetic purposes. Curiously, by using triisopropylsilyl triflate (entry 8) the stereoselectivity decreased.



Scheme 16. Intramolecular MBH reaction of **59**.

Table 3. MBH cyclization of substrates **59** to pyrroloazeopinones **60**.[a]

Entry	59	R^1	R^2	Acid Promoter	Conversion[b]	60 (Yield)	trans/cis[b]
1	**59f**	TBDPS	H	TMSOTf	100%		1:8
2[c]	**59f**	TBDPS	H	TMSOTf	67%		1:2.2
3[d]	**59f**	TBDPS	H	TMSOTf	—		
4	**59f**	TBDPS	H	$BF_3{\cdot}OEt_2$	100%		1:1.3
5	**59f**	TBDPS	H	$In(OTf)_3$	—		
6	**59f**	TBDPS	H	TfOH	72%		1:6
7	**59f**	TBDPS	H	TESOTf	100%	**60f** (68%)	only *cis*
8	**59f**	TBDPS	H	TIPSOTf	100%		1:15
9	**59a**	Bn	H	TESOTf		**60a** (30%)	1:1
10	**59b**	PMB	H	TESOTf	100%[e]		
11	**59c**	Piv	H	TESOTf	100%	**60c** (56%)	1:1.2
12	**59c**	Piv	H	TMSOTf	56%		1:1.2
13	**59c**	Piv	H	TfOH	45%		1:1.4
14	**59d**	Bz	H	TESOTf		**60d** (63%)	1.7:1
15	**59e**	TBS	H	TESOTf	100%[e]		
16	**59g**	H	Et	TESOTf	—		
17	**59h**	Me_2C		TESOTf	100%[e]		

[a]All the reactions were performed in CH_3CN (except entry 2), using Me_2S as the nucleophile (except entry 3), from –35 ºC to room temperature, for an overall time of 4 h.

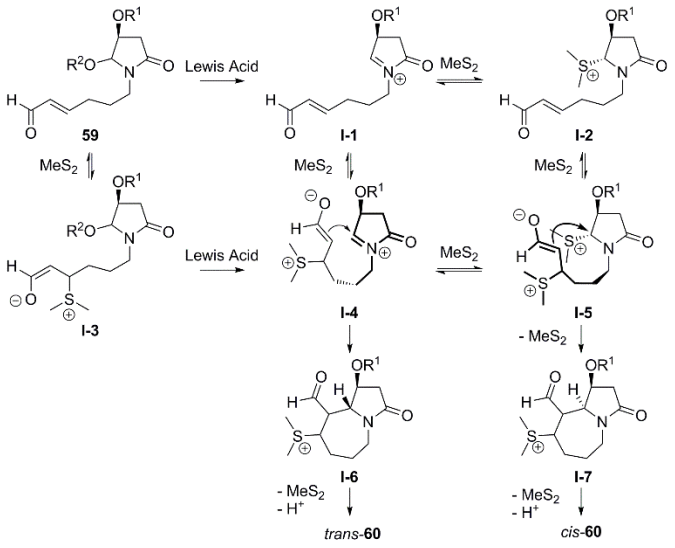
[b]Determined by ^1H NMR analysis of the crude material. [c]Reaction performed in CH_2Cl_2. [d]DABCO was used as the nucleophile.

[e]Converted to the corresponding free alcohols.

Then, the conditions of entry 7 were applied to the rest of derivatives **59**. We observed that the substrates bearing acid sensitive functionalizations (entries 10, 15 and 17) did not survive to the MBH reaction conditions and transformed into the corresponding free alcohol, which did not evolve to the azabicyclic product. Consistently, from alcohol **59g** cyclization products were not observed either (entry 16). On the contrary, the benzyl derivative **59a** furnished the azabicycle **60a**, albeit in quite low yield and without any stereoselectivity (entry 9), while the ester derivatives **59c** and **59d** (entries 11 and 14) gave reasonable yields of cyclization product but the stereodifferentiation was still very low. Two complementary acid promoters, TMSOTf and and TfOH, assayed on the pivaloate **59c** did not give better results (entries 12 and 13).

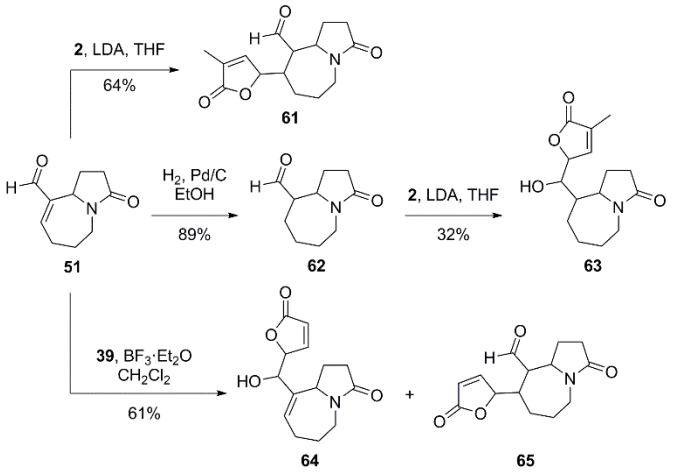
The relative configuration of **60f** was assigned by ^1H NMR analysis, including NOE experiments. Although the minor isomer could not be isolated, the spectrum of a mixture of both isomers

showed a clear correlation with the data reported for the acetates *cis* and *trans*-**46**. Moreover, for the major isomer, selective irradiation of H-1 produced a very strong enhancement of the signal corresponding to H-9a, which is only compatible with its *cis* relative geometry. The fact that for the cyclization of **59f** the face selectivity was opposite to the expected one evidences that the intramolecular MBH reaction occurs through a quite complex mechanistic pathway. For this process, it is broadly accepted that the formation of the new carbon-carbon bond requires the conjugate addition of the nucleophile to effect vinylogous enolization of the α,β-unsaturated aldehyde, followed by quenching of the zwitterionic adduct with an electrophile, and then proton transfer and elimination of the nucleophilic promoter.[32] However, since the cyclization of **59** requires the use of nucleophile and Lewis acid amounts superior to the stoichiometric ones, a series of equilibriums may be at play (Scheme 17). The *a priori* expected pathway would imply the formation of the acyliminium intermediate **I-4**, accessible from **I-1** or **I-3**, respectively resulting from the acid promoted generation of the electrophile or the vinilogous enolization by Me_2S addition. Based on steric effect considerations, the cyclization of **I-4** should deliver the *trans* isomer of **60**, produced by attack of the enolate to the less hindered face of the acyliminium ion. However, there is also the possibility that the iminium intermediates **I-1** and/or **I-4** react with the external nucleophile ultimately leading to a new species **I-5**, which would then evolve to the *cis* isomer of **60**. This intricate mechanistic landscape may account for the apparently random stereoselectivity observed in the MBH cyclization of substrates **59** due to changes (even quite subtle) on the substrate, Lewis acid or solvent. In any case, we concluded that azabicycle **60f**, available in 68% yield as a unique isomer under the conditions of entry 7, was the intermediate of choice to continue the synthetic studies towards the targeted alkaloids, but the following steps of the sequence were previously explored with the racemic model compounds lacking the substituent at C-1.



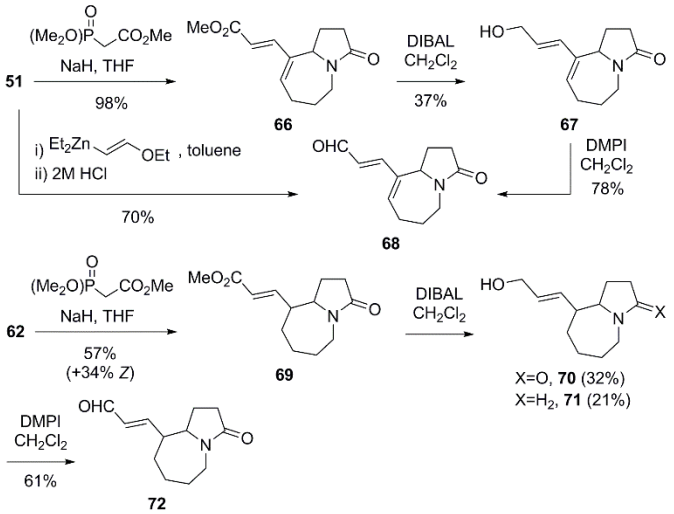
Scheme 17. Mechanistic pathways for the MBH cyclization of **59**.

Surprisingly, the reaction between the model aldehyde **51** and the lithium enolate of furanone **2** furnished exclusively the 1,4-addition product **61** (Scheme 18) and, when the reaction was assayed on aldehyde **62**, prepared by catalytic hydrogenation of the carbon-carbon double bond, the expected alcohol **63** was obtained in quite low yield. Moreover, both **61** and **63** were isolated as complex mixtures of various diastereoisomers. The Mukayama aldol protocol was also intended by addition of silyloxyfuran **39** under Lewis acid catalysis,[33] but the best conditions found led to a mixture of the two regioisomers **64** and **65**, wherein the 1,4-addition product predominated, and the isolated fractions of each regioisomer contained as well several diastereoisomers. Analogous reactions using enones **53** or **48** as the substrate met also with failure and only 1,4-addition products were occasionally detected.



Scheme 18. Model studies for the introduction of the furanone fragment to the azabicyclic aldehyde **51**.

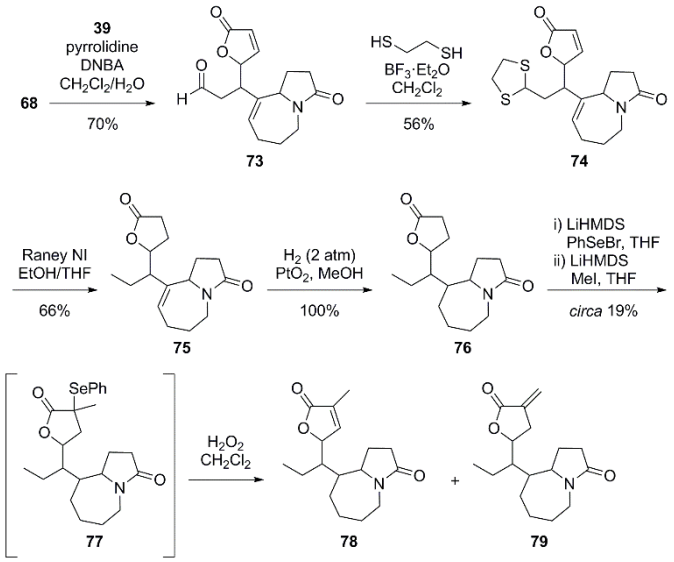
We next decided to attempt the two-carbon homologation of aldehydes **51** and **62** in order to assay the Mukayama-Michael methodology to introduce the furanone fragment (Scheme 19). Horner-Wadsworth-Emmos (HWE) reaction of the α,β-unsaturated aldehyde **51** furnished the expected ester in excellent yield and *E* stereoselectivity, but the subsequent reduction met with chemoselectivity problems, caused by partial reduction of the lactam and carbon-carbon double bonds, and dienol **67** was isolated in a poor 37% yield, as the best result, when the reduction was performed with DIBAL-H in CH_2Cl_2 at –78 ºC. Oxidation of **67** with DMPI rendered the α,β,γ,δ-unsaturated aldehyde **68** in 78% yield. A parallel set of transformations was applied to aldehyde **62**. From this substrate, the HWE alkenylation resulted less stereoselective and, besides the *E* ester **69**, a minor quantity of its *Z* isomer was also formed. From the subsequent DIBAL-H



Scheme 19. Two-carbon homologation of aldehydes **51** and **62**.

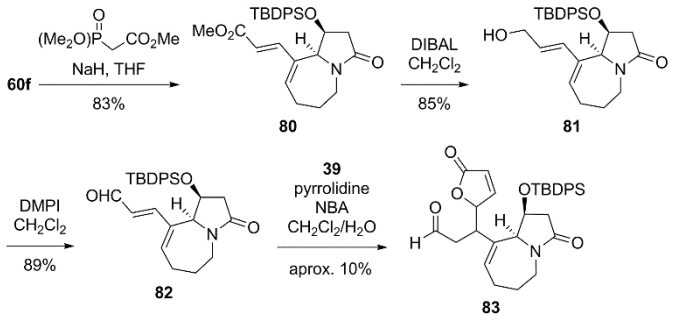
reduction of **69**, lactam **70** and amine **71** could be isolated in 32% and 21% yield, respectively, provided that the reaction was quenched before complete consumption of the starting material, 30% of which being recovered. Hydroxylactam **70** was then oxidized to the corresponding aldehyde **72** that was extremely unstable. Hence, the model studies for the addition of the furanone to the β-carbonyl position were performed with the α,β,γ,δ-unsaturated aldehyde **68** as the electrophile partner. The synthesis of this aldehyde could be substantially improved by reaction of **51** with (*E*)-(2-ethoxyvinyl)(ethyl)zinc, prepared *in situ* from ethoxyacetylene, $BH_3{\cdot}SMe_2$ and Et_2Zn,[34] a procedure leading directly to **68** in 70% yield.

The conjugate addition of the furanone moiety to aldehyde **68** was studied in deep by modification of all the parameters involved. Besides the trimethylsilyloxyfurane **19,** its 5-methyl derivative and their triisopropylsilyl analogues were also explored as nucleophiles, using always an excess amount going from 20% to threefold. The experiments were performed employing the chiral McMillan's organocatalyst **40** or pyrrolidine, in combination with three different acids, DNBA, TfOH and TFA. Most reactions were run in CH_2Cl_2, but toluene was also assayed, one or two equivalents of water were added to the reaction medium, and a temperature range from –70 ºC to room temperature was covered. The best conditions found involved the use of 1.5 equivalent of silyloxyfurane **19** in CH_2Cl_2, in the presence of pyrrolidine, DNBA and 2 equivalents of water, from –20 ºC to room temperature for 72 h, and allowed the isolation of the adduct **73** as a 4.3:1.9:1 mixture of three diastereoisomers in 70% overall yield (Scheme 20). Deoxygenation of **73** was accomplished by formation of dithiane **74**,[35] followed by desulfuration by treatment with Raney Ni,[36] which was concomitant with the reduction of the conjugated carbon-carbon double bond. Subsequent hydrogenation of the remaining alkene functionality proceeded in quantitative yield to furnish **76**, still as a mixture of three stereoisomers. To complete the sessilifoliamides B and C skeleton, it remained only attaching the methyl group at C-13. This endeavor was achieved by an α-selenylation/methylation/oxidation-elimination protocol that delivered a mixture of lactones **78** and **79**. Since we were dealing with model compounds and very small quantities of materials, further efforts to improve the efficiency of these last steps or to separate and independently characterize the regioisomers **78** and **79** were not made.



Scheme 20. Model studies for the introduction of the furanone fragment to the azabicyclic aldehyde **68**.

Next, our efforts were focused on applying the same sequence of reactions to the enantiomerically pure aldehyde **60f** (Scheme 21). The straight conversion of **60f** into the two-carbon homolog **82** by reaction with (*E*)-(2-ethoxyvinyl)(ethyl)zinc was inefficient in this case, lacking reproducibility. However, the HWE reaction took place with complete stereoselectivity, providing ester **80** in 83% yield and the conversion of **80** to the aldehyde **82**, through reduction to the alcohol followed by oxidation with DMPI, was accomplished in good yield. Unfortunately, when the above conditions for the Mukayama-Michael reaction optimized for the model aldehyde **68** were applied to **82** the expected addition product **83** was formed in very low yield. ^{1}H NMR analysis of the reaction evolution of an experiment performed in CD_2Cl_2 as the solvent (Figure 3), evidenced that the rate of formation of **83** is lower than its decomposition. Despite the reaction was attempted under modified conditions, we were unable to set up a synthetically useful method for the preparation of **83** and our efforts were directed to alternative



Scheme 21. Attempted synthesis of **83**.

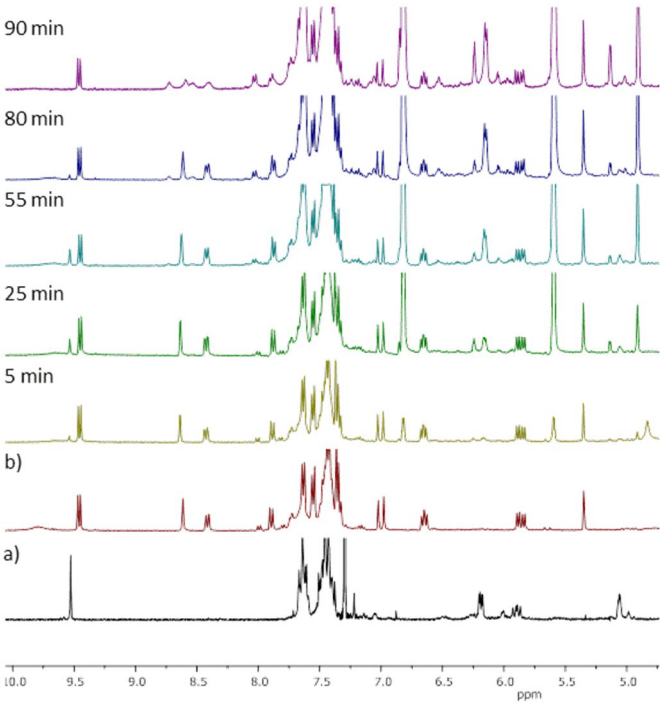


Figure 3. ^{1}H NMR analysis (250 MHz, CD_2Cl_2) of the reaction evolution between **82** and **39**; a) fragment of the ^{1}H NMR spectrum of adduct **83**; b) Reaction mixture at time 0 min.

3. Conclusions

In summary, we have explored an original synthetic approach to the *Stemona* alkaloids stenine and sessilifoliamides B and C based on the early construction of the pyrroloazepine core (rings A and B) and posterior addition of the furanone (ring D) and the ethyl chain at C-10. The formation of the azabicyclic nucleus through an intramolecular Morita-Baylis-Hillman reaction of a properly substituted pyrrolidone has been extensively investigated by modifications on the substrate and all the parameters involved in the process. As a result of these studies, an efficient protocol in terms of yield and stereoselectivity has been developed. Despite many alternative tactics were explored, insuperable difficulties found in the last synthetic steps have frustrated the completion of the syntheses. However, along the way, a plethora of new compounds has been prepared, some of them containing the full skeleton of the targeted alkaloids, which can be useful for future synthetic applications.

4. Experimental section

4.1. General remarks

Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying agents. All reactions were performed avoiding moisture by standard procedures and under nitrogen atmosphere. Flash column chromatography was performed using silica gel (230-400 mesh) unless otherwise indicated. ^{1}H NMR and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, 400 and 100 MHz, 360 and 90 MHz, or 500 and 125 MHz. Proton and carbon chemical shifts are reported in ppm (δ) ($CDCl_3$, δ 7.26 for ^{1}H; $CDCl_3$, δ 77.2 for ^{13}C). NMR signals were assigned with the help of COSY, HSQC, HMBC, and NOESY experiments. Melting points were determined on hot stage and are uncorrected. Optical rotations were measured at 22 ± 2 °C. This section need to include the type of elemental analyzer and the name of the analytical lab.

*4.2. (6S,7R,8S)-6-Hydroxymethyl-8-triisopropylsilyloxy-1-azabicyclo[5.3.0]decan-2-one (**6**)*

A solution of $LiBH_4$ in THF (2M, 12.0 mL, 23.7 mmol) was added to a solution of ester **1** (2.3 g, 5.9 mmol) in dry diethyl ether (100 mL) and the mixture was stirred at room temperature overnight. The excess of $LiBH_4$ was quenched by slow addition of saturated aqueous NH_4Cl (10 mL). The volatiles were removed under vacuum and the residue was extracted with CH_2Cl_2 (2x100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (hexanes/EtOAc,1:1, to EtOAc) afforded **6** as a white solid (2.1 g, 5.8 mmol, 99%): Mp 80-85 ºC (hexanes/EtOAc); $[\alpha]_D$ +11 (*c* 1.15, $CHCl_3$); IR (ATR) 3414, 2940, 2861, 1617, 1462, 1431, 1354, 1137, 1159, 1118, 1031 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.51 (m, 1H, H-8), 3.74 (br s, 1H, H-7), 3.69 (dt, $J_{10,10}$ = 11.8 Hz, $J_{10,9}$ = 7.7 Hz, 1H, H-10), 3.59 (dd, $J_{1',1'}$ = 10.7 Hz, $J_{1',6}$ = 6.3 Hz, 1H, H-1'), 3.46 (dd, $J_{1',1'}$ = 10.7 Hz, $J_{1',6}$ = 6.8 Hz, 1H, H-1'), 3.36 (ddd, $J_{10,10}$ = 11.9 Hz, $J_{10,9}$ = 7.9 Hz, $J_{10,9}$ = 5.6 Hz, 1H, H-10), 3.17 (br s, 1H, OH), 2.43 (m, 2H, 2H-3); 2.12 (m, 3H, H-5, H-6, H-9), 1.65 (m, 4H, 2H-4, H-5, H-9), 1.02 (br s, 21H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.6 (CO), 78.6 (C-8), 71.1 (C-7), 60.3 (C-1'), 46.0 (C-10), 40.9 (C-6), 38.6 (C-3), 33.6 (C-9), 33.0 (C-5), 19.0 (C-4), 18.5 (CH*Me$_3$*), 12.6 (*C*HMe$_3$); MS *m/z* (ESI+, MeOH): 378 (MNa^+); HRMS (ESI+) calcd for [$C_{19}H_{37}NO_3SiH^+$]: 356.2621, found: 356.2613.

*4.3. (6S,7R,8S)-2-Oxo-8-triisopropylsilyloxy-1-azabicyclo[5.3.0]decan-6-carbaldehyde (**7**)*

A solution of DMPI in CH_2Cl_2 (15 wt%, 11.4 mL) was added dropwise to a solution of alcohol **6** (1.8 g, 5.0 mmol) in dry CH_2Cl_2 (90 mL) under a nitrogen atmosphere and the mixture was stirred at room temperature for 2 h. To eliminate the excess of oxidant, the mixture was quenched with 7 mL of a solution prepared by addition of $Na_2S_2O_3$ (17 g) to saturated aqueous $NaHCO_3$ (90 mL). The phases were separated and the aqueous one extracted with CH_2Cl_2 (2x50 mL).The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexanes/EtOAc, 1:1) to give **7** as a white solid (1.6 g, 4.5 mmol, 90%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.74 (s, 1H, H-1'), 4.60 (td, $J_{8,9}$ = 6.6 Hz, $J_{8,7}$ = 5.2 Hz, 1H, H-8), 3.91 (ddd, $J_{10,10}$ = 11.8 Hz, $J_{10,9}$ = 8.2 Hz, $J_{10,9}$ = 4.5 Hz, 1H, H-10), 3.71 (br d, $J_{7,8}$ = 5.2 Hz, 1H, H-7), 3.36 (ddd, $J_{10,10}$ = 11.8 Hz, $J_{10,9}$ = 8.8 Hz, $J_{10,9}$ = 7.0 Hz, 1H, H-10), 2.83 (br t, $J_{6,5}$ = 3.4 Hz, 1H, H-6), 2.55 (m, 3H, 2H-3, H-5), 2.12 (m, 1H, H-9), 1.80 (m, 4H, 2H-4, H-5, H-9), 1.04 (br s, 21H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 203.3 (C-1'), 173.7 (CO), 77.8 (C-8), 67.7 (C-7), 50.8 (C-6), 45.6 (C-10), 38.2 (C-3), 33.6 (C-9), 31.4 (C-5), 20.5 (C-4), 18.5 (CH*Me$_3$*), 12.7 (*C*HMe$_3$). To avoid epimerization, aldehyde **7** was immediately processed to the next step.

*4.4. (6S,7R,8S)-6-{(1S)-1-Hydroxy-[(2R)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl]methyl}-8-triisopropylsilyloxy-1-azabicyclo[5.3.0]decan-2-one (**8**) and (6R,7R,8S)-6-[(1-Hydroxy)(4-methyl-5-oxo-2,5-dihydrofuran-2-yl)methyl]-8-triisopropylsilyloxy-1-azabicyclo[5.3.0]decan-2-one (**11**)*

LDA (2M in THF, 1.0 mL, 2.1 mmol) was added dropwise to a solution of 2(5*H*)-furanone **2** (183 µL, 2.1 mmol) in dry THF (25 mL) at –78 ºC under nitrogen atmosphere. The mixture was stirred for 5 min and then a solution of aldehyde **7** (750 mg, 2.1 mmol) in dry THF (10 mL) was added dropwise. The reaction mixture was stirred at –78 ºC for 1 h. The reaction was quenched by the slow addition of saturated aqueous NH_4Cl (10 mL). The layers were separated and the aqueous one was extracted with EtOAc (2x20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvents evaporated to dryness. The crude material was purified by column chromatography (hexanes/EtOAc, 1:1, to EtOAc) to afford compound **8** as a white solid (683 mg, 1.5 mmol, 72%): Mp 148-152 ºC (EtOAc/hexane); $[\alpha]_D$ +35 (*c* 1.00, $CHCl_3$); IR (ATR) 3339, 2932, 2862, 1757, 1617,1460, 1352, 1212, 1161, 1095, 1059, 1037 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.99 (q, $J_{3'',2''}$ = $J_{3'',Me}$ = 1.5 Hz, 1H, H-3''), 4.96 (m, 1H, H-2''), 4.91 (td, $J_{8,9}$ = 6.1 Hz, $J_{8,7}$ = 3.8 Hz, 1H, H-8), 4.11 (dd, $J_{1',6}$ = 10.1 Hz, $J_{1',2''}$ = 2.7 Hz, 1H, H-1'), 3.82 (m, 2H, H-10, OH), 3.74 (br d, $J_{7,8}$ = 3.8 Hz, 1H, H-7), 3.44 (dt, $J_{10,10}$ = 11.8 Hz, $J_{10,9}$ = 8.1 Hz, 1H, H-10), 2.60 (m, 2H, 2H-3), 2.25 (m, 1H, H-9), 2.18 (br d, $J_{6,1'}$ = 10.1 Hz, 1H, H-6), 1.93 (t, $J_{Me,3''}$ = $J_{Me,2''}$ = 1.5 Hz, 3H, CH_3), 1.70 (m, 5H, 2H-4, 2H-5, H-9), 1.04 (br s, 21H, 3 CH, 6 CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.9 (CO), 173.5 (CO), 144.0 (C-3''), 132.5 (C-4''), 82.0 (C-2''), 78.4 (C-8), 71.9 (C-7), 67.6 (C-1'), 46.0 (C-10), 40.3 (C-6), 37.8 (C-3), 33.2 (C-9), 32.6 (C-5), 18.6 (C-4), 17.9 (CH*Me$_3$*), 12.1 (*C*HMe$_3$), 10.8 (CH_3); HRMS (ESI+) calcd for [$C_{24}H_{41}NO_5SiH^+$]: 452.2832, found: 452.2831.

Eventually, a small quantity of aldehyde **11**, of unknown configuration at C-1' and C-2'', was also isolated: Mp 146-150 ºC (hexanes/EtOAc); $[\alpha]_D$ –36.0 (*c* 1.00, $CHCl_3$); IR (ATR) 3372, 2935, 2861, 1759, 1611, 1456, 1380, 1306, 1188, 1092, 1029 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.00 (q, $J_{3'',2''}$ = $J_{3'',Me}$ = 1.6 Hz, 1H, H-3''), 5.02 (m, 1H, H-2''), 4.67 (m, 1H, H-8), 3.93 (td, $J_{1',6}$ = $J_{1',OH}$ = 8.5 Hz, $J_{1',2''}$ = 1.6 Hz, 1H, H-1'), 3.86 (s, 1H, H-7), 3.77 (dt, $J_{10,10}$ = 11.6 Hz, $J_{10,9}$ = 8.1 Hz, 1H, H-10), 3.50 (ddd, $J_{10,10}$ =

11.6 Hz, $J_{10,9}$ = 8.4 Hz, $J_{10,9}$ = 5.4 Hz, 1H, H-10), 2.40 (m, 4H, 2H-3, H-6, H-9), 2.06 (d, $J_{OH,1'}$ = 8.5 Hz, 1H, OH), 1.92 (t, $J_{Me,3''}$ = $J_{Me,2''}$ = 1.6 Hz, 3H, CH_3), 1.63 (m, 5H, 2H-4, 2H-5, H-9), 1.02 (br s, 21H, 3 CH, 6CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.8 (CO), 173.7 (CO), 147.3 (C-3'), 131.1 (C-4'), 81.8 (C-2'), 79.2 (C-8), 73.0 (C-7), 67.9 (C-1'), 46.4 (C-10), 42.3 (C-6), 38.3 (C-3), 33.3/32.5 (C-5/C-9), 19.0 (C-4), 17.9 (CH*Me*$_3$), 12.0 (*C*HMe$_3$), 10.9 (CH_3).

4.5. *(6S,7R,8S)-8-Hydroxy-6-{(1S)-hydroxy-[(2R)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl]methyl}-1-azabicyclo[5.3.0]decan-2-one (**9**)*

Trifluoromethansulfonic acid (75 μL, 0.82 mmol) was added to a solution of alcohol **8** (95 mg, 0.21 mmol) in dry CH_2Cl_2 (4 mL) and the mixture was stirred at room temperature for 5 min. The solvent was partially removed under reduced pressure and the resulting solution was purified by column chromatography (EtOAc) to deliver diol **9** as a white solid (50 mg, 0.17 mmol, 81%): Mp 195-198 ºC (EtOAc/pentane); $[\alpha]_D$ +17 (*c* 1.45, MeOH); IR (ATR) 3358, 2970, 2882, 1757, 1597,1456, 1326, 1287, 1193, 1090, 1047, 982 cm^{-1}; ^{1}H NMR (250 MHz, CD_3OD) δ 7.33 (q, $J_{3'',2''}$ = $J_{3'',Me}$ = 1.7 Hz, 1H, H-3''), 5.14 (m, 1H, H-2''), 4.76 (ddd, $J_{8,9}$ = 6.3 Hz, $J_{8,9}$ = 5.6 Hz, $J_{8,7}$ = 3.4 Hz, 1H, H-8); 4.03 (dd, $J_{1',6}$ = 10.4 Hz, $J_{1',2''}$ = 3.2 Hz, 1H, H-1'), 3.87 (br d, $J_{7,8}$ = 3.4 Hz, 1H, H-7), 3.82 (m, 1H, H-10), 3.42 (m, 1H, H-10), 2.62 (m, 2H, 2H-3); 2.37 (m, 1H, H-9), 2.20 (m, 2H, H-5, H-6), 1.94 (t, $J_{Me,3''}$ = $J_{Me,2''}$ = 1.7 Hz, 3H, CH_3), 1.75 (m, 4H, 2H-4, H-5, H-9); ^{13}C NMR (62.5 MHz, CD_3OD) δ 177.0 (CO), 147.9 (C-3''), 133.9 (C-4''), 85.0 (C-2''), 79.3 (C-8), 73.8 (C-7), 69.6 (C-1'), 48.1 (C-10), 43.0 (C-6), 39.5 (C-3), 34.3/33.8 (C-5/C-9), 20.5 (C-4), 11.6 (CH_3); MS *m/z* (ESI+, MeOH): 318 (MNa^+); HRMS (ESI+) calcd for [$C_{15}H_{21}NO_5H^+$]: 296.1498, found: 296.1505.

4.6. *Methyl (6S,7R,8S)-8-triisopropylsilyloxy-1-azabicyclo[5.3.0]decan-6-carboxylate (**12**)*

A solution of DIBAL-H (1M in hexane, 208 μL, 0.20 mmol) was added dropwise to a solution of **1** (20 mg, 0.05 mmol) in dry toluene (2 mL) under nitrogen atmosphere and the mixture was stirred at room temperature for 12 h. The excess of hydride was eliminated by the slow addition of $Na_2SO_4{\cdot}10H_2O$, the mixture filtered through *Celite*® and the solvent was removed under vacuum. Purification by column chromatography (hexanes/EtOAc, 1:1) led to recovering of unreacted material (10 mg, 0.03 mmol, 50%) and afforded amine **12** as a yellowish oil (5 mg, 0.01 mmol, 7%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.38 (br d, $J_{8,9}$ = 5.2 Hz, 1H, H-8), 3.64 (s, 3H, CH_3), 3.09 (m, 1H, H-10), 2.98 (m, 1H, H-10), 2.90 (dt, $J_{6,5}$ = 7.0 Hz, $J_{6,7}$ = 3.9 Hz, 1H, H-6), 2.72 (dd, $J_{7,6}$ = 3.9 Hz, $J_{7,8}$ = 1.6, 1H, H-7), 2.64 (ddd, $J_{2,2}$ = 12.0 Hz, $J_{2,3}$ = 8.6 Hz, $J_{2,3}$ = 5.6 Hz, 1H, H-2), 2.27 (ddd, $J_{2,2}$ = 12.0 Hz, $J_{2,3}$ = 9.0 Hz, $J_{2,3}$ = 5.2 Hz, 1H, H-2), 2.00 - 1.40 (m, 8H, 2H-3, 2H-4, 2H-5, 2H-9), 1.03 (br s 21H, 3 CH, 6 CH_3); ^{13}C RMN (62.5 MHz, $CDCl_3$) δ 175.1 (CO), 78.0 (C-8), 75.7 (C-7), 57.1/55.0 (C-2/C-10), 51.2 (OCH_3), 46.5 (C-6), 34.7 (C-3), 30.0/29.5 (C-5/C-9), 24.1 (C-4), 18.0 (CH*Me*$_3$), 12.2 (*C*HMe$_3$).

4.7. *(6S,7R,8S)-6-{(1S)-Hydroxy-[(2R)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl]methyl}-8-imidazolylthiocarbonyloxy-1-azabicyclo[5.3.0]decan-2-one (**14**) and (1R,2aR,2a^{1}R,8aS)-1-[(R)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl]octahydro-2-oxa-4a-azacyclopenta[cd]azulen-5(1H)-one (**15**)*

A solution of TCDI (72 mg, 0.40 mmol) in dry THF (1 mL) was added to a solution of diol **9** (30 mg, 0.10 mmol) in dry THF (1 mL) and the mixture was stirred at room temperature for 4 h. The solvent was removed under vacuum and the residue was purified by column chromatography (EtOAc) to afford **14** (37 mg, 0.09 mmol, 90% yield) as a yellowish oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.35 (s, 1H, H-Im), 7.60 (t, J = 1.4 Hz, 1H, H-Im), 7.07 (q, $J_{3'',2''}$ = $J_{3'',Me}$ = 1.5 Hz, 1H, H-3''), 7.03 (dd, *J* = 1.6 Hz, *J'* = 0.7 Hz, 1H, H-Im), 6.07 (br d, $J_{8,9}$ = 6.3 Hz, 1H, H_8), 5.25 (br s, 1H, OH), 4.98 (m, 1H, H-2''), 4.21 (dd, $J_{1',6}$ = 10.6 Hz, $J_{1',2''}$ = 3.0 Hz, 1H, H-1'), 4.16 (br s, 1H, H-7), 3.75 (m, 2H, 2H-10), 2.85 (m, 1H, H-9), 2.58 (m, 3H, 2H-3, H-6), 2.10 (m, 2H), 1.95 (t, $J_{Me,3''}$ = $J_{Me,2''}$ = 1.5 Hz, 3H, CH_3), 1.75 (m, 3H). Compound **14** is unstable and undergoes spontaneous cyclization to ether **15**, which was isolated as a yellowish oil. $[\alpha]_D$ +34 (*c* 1.15, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.06 (q, $J_{3',2'}$ = $J_{3',Me}$ = 1.8 Hz, 1H, H-3'), 4.87 (m, 2H, $H_{2'}$, H-2a), 4.35 (dd, $J_{1,8a}$ = 7.2 Hz, $J_{1,2'}$ = 5.0 Hz, 1H, H-1), 3.81 (ddd, $J_{4,10}$ = 11.1 Hz, $J_{4,3}$ = 8.8 Hz, $J_{4,3}$ = 1.8 Hz, 1H, H-4), 3.64 (t, $J_{2a',2a}$ = $J_{2a',2a}$ = 5.6 Hz, 1H, H-2a^1), 3.32 (td, $J_{4,4}$ = $J_{4,3}$ = 11.1 Hz, $J_{4,3}$ = 6.6 Hz, 1H, H-4), 2.42 (m, 2H, 2H-6), 2.08 (m, 2H, H-8a, H-3), 1.92 (t, $J_{Me,3'}$ = $J_{Me,2'}$ = 1.8 Hz, 3H, CH_3), 1.80 (m, 3H, H-3, H-7, H-8), 1.45 (m, 2H, H-7, H-8); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.3 (CO), 171.5 (CO), 146.5 (C-3'), 132.1 (C-4'), 87.1 (C-2a^1), 86.1/83.1 (C-5/C-2a), 65.9 (C-1), 44.7 (C-4), 43.7 (C-8a), 34.2 (C-6), 30.7 (C-3), 27.8/19.9 (C-7/C-8), 11.3 (CH_3); MS *m/z* (ESI+, MeOH): 300 (MNa^+); HRMS (ESI+) calcd for [$C_{15}H_{19}NO_4H^+$]: 278.1392, found: 278.1388.

4.8. *(6S,7R,8S)-6-{(1S)-Methoxymethoxy-[(2R)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl]methyl}-8-triisopropylsilyloxy-1-azabicyclo[5.3.0]decan-2-one (**16**)*

MOMBr (90 μL, 1.10 mmol) was added to a solution of NaI (135 mg, 0.90 mmol) in dry DME (2 mL). Then, ^{i}Pr$_2$NEt (215 μL, 1.23 mmol) and a solution of alcohol **9** (100 mg, 0.22 mmol) in dry DME (3 mL) was added and the reaction mixture was heated at the reflux temperature overnight. The volatiles were removed under vacuum and the residue was diluted with CH_2Cl_2 (10 mL), washed with saturated aqueous $NaHCO_3$ (5 mL), dried over anhydrous Na_2SO_4 and the solvents evaporated to dryness. Purification of the crude material by column chromatography (EtOAc) afforded ether **16** as a yellowish oil (108 mg, 0.22 mmol, 98%): $[\alpha]_D$ +58 (*c* 2.85, $CHCl_3$); IR (ATR) 2936, 2863, 1759, 1637, 1460, 1422, 1344, 1158, 1060 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.99 (q, $J_{3'',2''}$ = $J_{3'',Me}$ = 2.0 Hz, 1H, H-3''), 5.03 (m, 1H, H-2''), 4.91 (td, $J_{8,9}$ = 7.0 Hz, $J_{8,7}$ = 5.2 Hz, 1H, H-8), 4.52 (s, 2H, OCH_2), 3.99 (dd, $J_{1',6}$ = 9.5 Hz, $J_{1',2''}$ = 2.0 Hz, 1H, H-1'), 3.92 (ddd, $J_{10,10}$ = 11.8 Hz, $J_{10,9}$ = 8.8 Hz, $J_{10,9}$ = 3.2 Hz, 1H, H-10), 3.22 (s, 3H, OCH_3), 3.15 (m 1H, H-10), 2.55 (m, 2H, 2H-3), 2.30 (br d, $J_{6,1'}$ = 9.5 Hz, 1H, H-6), 2.10 (m, 2H, H-9, H-5), 1.92 (t, $J_{Me,3''}$ = $J_{Me,2''}$ = 2.0 Hz, 3H, CH_3), 1.65 (m, 4H, 2H-4, H-5, H-9), 1.03 (br s, 21H, 3 CH, 6 CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.9 (CO), 144.1 (C-3''), 132.9 (C-4''), 99.4 (OCH_2), 82.4 (C-2''), 77.7 (C-8), 77.4 (C-1'), 71.4 (C-7), 56.8 (OCH_3), 46.0 (C-10), 39.0 (C-6), 38.4 (C-3), 33.8/33.3 (C-5/C-9), 19.0 (C-4), 18.4 (CH*Me*$_3$), 12.6 (*C*HMe$_3$), 11.2 (CH_3); HRMS (ESI+) calcd for [$C_{26}H_{45}NO_6SiH^+$]: 496.3094, found: 496.3088.

4.9. *(6S,7R,8S)-8-Hydroxy-6-[(Z)-4-methyl-5-oxo-5H-furan-2-ylidenmethyl]-1-azabicyclo[5.3.0]decan-2-one (**17**)*

A solution of TBAF in THF (1M, 87 μL, 0.09 mmol) was added to an ice-cooled solution of **16** (45 mg, 0.09 mmol) in dry THF (1 mL) and the mixture was stirred at 0 ºC for 45 min. The solvent was removed and the crude material purified by column chromatography (EtOAc) to deliver a white solid (16 mg, 0.06 mmol, 65%) identified as **17**: Mp 180-184 ºC (EtOAc); $[\alpha]_D$ –71 (*c* 1.15, $CHCl_3$); IR (ATR) 3246, 2855, 2364, 2331, 1759, 1592, 1462, 1433, 1320, 1254, 1181, 1151, 1046 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.00 (q, $J_{3'',Me}$ = 1.3 Hz, 1H, H-3''), 5.13 (d, $J_{1',6}$ = 10.0 Hz, 1H, H-1'), 4.14 (td, $J_{8,9}$ = 5.7 Hz, $J_{8,7}$ = 4.1 Hz, 1H, H-8), 4.16 (br d, $J_{7,8}$ = 4.1 Hz, 1H, H-7), 3.80 (m, 1H, H-10), 3.42 (br d, $J_{6,1'}$ = 10.0 Hz, 1H, H-6), 3.33 (dt, $J_{10,10}$ = 12.0 Hz, $J_{10,9}$ = 7.5 Hz, 1H, H-10), 2.55 (m, 2H, 2H-3), 1.99 (d, $J_{Me,3''}$ = 1.3 Hz, 3H,

CH_3), 1.82 (m, 6H, 2H-4, 2H-5, 2H-9); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.7 (CO), 171.3 (CO), 149.9 (C-2''), 138.1 (C-3''), 131.0 (C-4''), 111.0 (C-1'), 77.3 (C-8), 69.8 (C-7), 45.7 (C-10), 38.4 (C-3), 37.0 (C-6), 36.4/32.3 (C-5/C-9), 19.1 (C-4), 11.1 (CH_3); MS *m/z* (ESI+, MeOH): 300 (MNa^+); HRMS (ESI+) calcd for [$C_{15}H_{19}NO_4H^+$]: 278.1392, found: 278.1388.

4.10. *(6S,7R,8S)-8-Hydroxy-6-methoxymethoxy-[(2R)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl]methyl-1-azabicyclo[5.3.0]decan-2-one (**18**)*

To a stirred solution of **16** (108 mg, 0.22 mmol) in dry THF (5 mL) was added 3HF·Et_3N (720 μL, 4.40 mmol) under nitrogen atmosphere and the resulting mixture was heated at the reflux temperature for 3 h. The solvent was removed under reduced pressure and the residue was taken up with CH_2Cl_2. The solution was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under vacuum. The crude material was purified by column chromatography (EtOAc) to afford alcohol **18** as a white solid (67 mg, 0.20 mmol, 90%): Mp 134-137 ºC (EtOAc); $[\alpha]_D$ +36 (*c* 1.40, $CHCl_3$); IR (ATR) 3367, 2944, 2906, 1748, 1602, 1463, 1352, 1210, 1155, 1102, 1049, 1014 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.07 (q, $J_{3'',2''} = J_{3'',Me}$ = 2.1 Hz, 1H, H-3''), 5.11 (m, 1H, H-2''), 4.78 (td, $J_{8,9}$ = 7.7 Hz, $J_{8,7}$ = 6.1 Hz, 1H, H-8), 4.60 (d, J_{gem} = 6.5 Hz, 1H, 1H-acetal), 4.53 (d, J_{gem} = 6.5 Hz, 1H, 1H-acetal), 3.94 (ddd, $J_{10,10}$ = 11.4 Hz, $J_{10,9}$ = 8.9 Hz, $J_{10,9}$ = 2.5 Hz, 1H, H-10), 3.94 (dd, $J_{1',6}$ = 7.9 Hz, $J_{1',2''}$ = 2.1 Hz, 1H, H-1'), 3.62 (br d, $J_{7,8}$ = 6.1 Hz, 1H, H-7), 3.30 (s, 3H, OCH_3), 3.14 (td, $J_{10,10}$ = $J_{10,9}$ = 11.4 Hz, $J_{10,9}$ = 6.6 Hz, 1H, H-10), 2.50 (m, 2H, 2H-3), 2.15 (m, 2H, H-6, H-9), 1.94 (t, $J_{Me,3''} = J_{Me,2''}$ = 2.1 Hz, 3H, CH_3), 1.70 (m, 5H, 2H-4, 2H-5, H-9); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.3 (CO), 173.8 (CO), 144.7 (C-3''), 132.7 (C-4''), 98.6 (C-acetal), 82.9 (C-2''), 78.1 (C-1'), 76.2 (C-8), 69.3 (C-7), 56.7 (OCH_3), 45.8 (C-10), 38.2 (C-3), 37.0 (C-6), 33.9 (C-5), 32.7 (C-9), 19.0 (C-4), 11.2 (CH_3). Anal. calcd for $C_{17}H_{25}NO_6$: C, 60.16; H, 7.43; N: 4.13, found: C, 60.16; H, 7.48; N, 4.07.

4.11. *(6S,7R,8S)-8-Imidazolylthiocarbonyloxy-6-{(1S)-methoxymethoxy-[(2R)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl]methyl}-1-azabicyclo[5.3.0]decan-2-one (**19**)*

A solution of TCDI (63 mg, 0.36 mmol) in dry THF (1 mL) was added to a solution of alcohol **18** (30 mg, 0.09 mmol) in dry THF (1 mL) and the mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica Baker® (EtOAc) to afford **19** (36 mg, 0.08 mmol, 90%) as yellowish oil that presented low stability and was used in the next step without further purification: ^1H NMR (250 MHz, $CDCl_3$) δ 8.31 (t, *J* ~ 1.1 Hz, 1H, H-Im), 7.58 (dd, *J* = 1.7 Hz, *J'* = 1.2 Hz, 1H, H-Im), 7.07 (q, $J_{3'',2''} = J_{3'',Me}$ = 1.9 Hz, 1H, H-3''), 7.03 (dd, *J* = 1.7 Hz, *J'* = 0.9 Hz, 1H, H-Im), 6.13 (m, 1H, H-8), 5.06 (sext, $J_{2'',3''} = J_{2'',1'} = J_{2'',Me}$ = 1.9 Hz, 1H, H-2''), 4.60 (s, 2H, 2H-acetal), 4.10 (br s, 1H, H-7), 4.03 (dd, $J_{1',6}$ = 8.6 Hz, $J_{1',2''}$ = 1.9 Hz, 1H, H-1'), 3.92 (m, 1H, H-10), 3.55 (m, 1H, H-10), 3.31 (s, 3H, OCH_3), 2.60 (m, 4H, 2H-3, H-6, H-9), 2.00 (m, 2H), 1.95 (t, $J_{Me,3''} = J_{Me,2''}$ = 1.9 Hz, 3H, CH_3), 1.70 (m, 3H).

4.12. *(6S)-6-{(1S)-methoxymethoxy-[(2R)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl]methyl}-1-azabicyclo[5.3.0]dec-7-en-2-one (**20**)*

To a refluxing solution of **19** (35 mg, 0.08 mmol) in anhydrous toluene (8 mL) was added a solution of Bu_3SnH (from 21 μL, 0.08 mmol, to 314 μL, 1.17 mmol) and AIBN (from 5 mg, 0.03 mmol, to 19 mg, 0.12 mmol) in anhydrous toluene (8 mL), dropwise during a 12 h period using a dosing pump, and the reaction mixture was heated for two additional hours. Then, the solvent was removed under reduced pressure and the residue was purified by column chromatography (hexanes to EtOAc) to afford mixtures of **15**, **16** and **20**, in different relative proportions depending on the run. **20**: $[\alpha]_D$ +8 (*c* 1.00, $CHCl_3$); IR (ATR) 2925, 1756, 1614, 1443, 1342, 1210, 1152, 1096, 1021 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.18 (q, $J_{3'',2''} = J_{3'',Me}$ = 1.8 Hz, 1H, H-3''), 5.33 (m, 1H, H-8), 5.13 (dt, $J_{2'',1'}$ = 5.9 Hz, $J_{2'',3''} = J_{2'',Me}$ = 1.8 Hz, 1H, H-2''), 4.66 (d, J_{gem} = 6.8 Hz, 1H, 1H-acetal), 4.62 (d, J_{gem} = 6.8 Hz, 1H, 1H-acetal), 3.87 (m, 3H, H-1', 2H-10), 3.38 (s, 3H, OCH_3), 3.05 (m, 1H, H-6), 2.55 (m, 4H, 2H-3, H-5, H-9), 1.95 (t, $J_{Me,3''} = J_{Me,2''}$ = 1.8 Hz, 3H, CH_3), 1.85 (m, 4H, 2H-4, H-5, H-9); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.0 (CO), 171.2 (CO), 147.0 (C-3''), 141.3 (C-7), 131.6 (C-4''), 111.8 (C-8), 99.0 (C-acetal), 82.1 (C-1'), 80.9 (C-2''), 56.8 (OCH_3), 48.5 (C-10), 39.7 (C-6), 35.0 (C-3), 27.9/27.6 (C-5/C-9), 21.6 (C-4), 11.4 (CH_3).

4.13. *(6S,7R,8S)-8-(4-Fluorophenyloxy)thiocarbonyloxy-6-{(1S)-methoxymethoxy-[(2R)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl]methyl}-1-azabicyclo[5.3.0]decan-2-one (**21**)*

4-Fluorophenyl chlorothionoformate (25 μL, 176 μmol) and pyridine (21 μL, 264 μmol) were added to a solution of alcohol **18** (30 mg, 88 μmol) and *N*-hydroxysuccinimide (5 mg, 44 μmol) in anhydrous toluene (2 mL) and the mixture was heated under reflux for 1 h. After cooling, the solvent was evaporated in vacuum and the residue was purified by column chromatography (hexanes/EtOAc, 1:1) to afford **21** as oil (35 mg, 71 μmol, 80%): ^1H NMR (250 MHz, $CDCl_3$) δ 7.08 (d, $J_{H,F}$ = 6.6 Hz, 2H, 2H-Ar), 7.08 (d, $J_{H,F}$ = 5.7 Hz, 2H, 2H-Ar), 7.05 (t, $J_{3'',2''} = J_{3'',Me}$ = 2.0 Hz, 1H, H-3''), 5.90 (m, 1H, H-8), 5.06 (m, 1H, H-2''), 4.60 (d, J_{gem} = 6.1 Hz, 1H, 1H-acetal), 4.57 (d, J_{gem} = 6.1 Hz, 1H, 1H-acetal), 4.11 (br d, $J_{7,8}$ = 2.9 Hz, 1H, H-7), 4.01 (dd, $J_{1',6}$ = 9.1 Hz, $J_{1',2''}$ = 2.0 Hz, 1H, H-1'), 3.92 (m, 1H, H-10), 3.48 (m, 1H, H-10), 3.30 (s, 3H, OCH_3), 2.60 (m, 4H, 2H-3, H-6, H-9), 1.94 (t, $J_{Me,3''} = J_{Me,2''}$ = 2.0 Hz, 3H, CH_3), 1.80 (m, 5H, 2H-4, 2H-5, H-9); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 194.6 (CS), 173.4 (CO), 173.3 (CO), 160.7 (d, $J_{C,F}$= 236.3 Hz, C-Ar), 149.1 (d, $J_{C,F}$ = 3.2 Hz, C-Ar), 143.7 (C-3''), 132.7 (C-4''), 123.4 (d, $J_{C,F}$ = 8.3 Hz, C-Ar), 116.3 (d, $J_{C,F}$ = 22.6 Hz, C-Ar), 98.5 (C-acetal), 89.9 (C-8), 82.1 (C-2''), 76.7 (C-1'), 67.7 (C-7), 56.6 (OCH_3), 46.2 (C-10), 39.5 (C-6), 38.0 (C-3), 32.9 (C-5), 28.7 (C-9), 18.6 (C-4), 10.9 (CH_3).

4.14. *(6S,7R)-6-[(E)-4-Methyl-5-oxo-5H-furan-2-ylidenmethyl)-1-azabicyclo[5.3.0]decan-2-one (**22**)*

To a refluxing solution of Bu_3SnH (76 μL, 0.28 mmol) and AIBN (12 mg, 0.07 mmol) in anhydrous toluene (1.5 mL) in a schlenk vessel connected to a nitrogen line was added a solution of **21** (35 mg, 0.07 mmol) in anhydrous toluene (1.0 mL) and the mixture was heated under reflux for 3 h. Then, the solvent was removed under vacuum. Column chromatography of the residue (hexanes to EtOAc) afforded, as the unique identifiable product, an analytical sample of **22**: ^1H NMR (250 MHz, $CDCl_3$) δ 6.97 (c, $J_{3'',Me}$ = 1.8 Hz, 1H, H-3''), 5.14 (d, $J_{1',6}$ = 10.4 Hz, 1H, H-1'), 4.00 (t, $J_{7,8}$ = 7.0 Hz, 1H, H-7), 3.80 (m, 1H, H-10), 3.18 (m, 2H, H-6, H-10), 2.53 (m, 2H, 2H-3), 2.20 (m, 1H, H-8), 1.99 (d, $J_{Me,3''}$ = 1.8 Hz, 3H, CH_3), 1.75 (m, 7H, 2H-4, 2H-5, H-8, 2H-9); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.8 (CO), 170.5 (CO), 149.6 (C-2''), 137.5 (C-3''), 130.2 (C-4''), 110.8 (C-1'), 61.0 (C-7), 47.7 (C-10), 38.9 (C-6), 38.0 (C-3), 35.8/23.4 (C-5/C-9), 32.7 (C-8), 18.7 (C-4), 10.6 (CH_3).

4.15. *5,5'-Bis{(S)-(methoxymethoxy)[(9S,9aS)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-9-yl]methyl}-3,3'-dimethyl-[3,3'-bifuran]-2,2'(3H,3'H)-dione (**23**)*

A solution of Bu_3SnH (43 μL, 0.16 mmol) and AIBN (7 mg, 0.04 mmol) in anhydrous toluene (1 mL) and a solution of **21** (20 mg, 0.04 mmol) in anhydrous toluene (1 mL) were simultaneously

added to refluxing anhydrous toluene (1 mL) in a schlenk vessel connected to a nitrogen line, dropwise, during a 12 h period using a dosing pump. After the addition, the reaction mixture was heated for two additional hours. Then, the solvent was removed under vacuum. Column chromatography of the residue (hexanes to EtOAc) afforded, as the unique identifiable product, an analytical sample of a mixture of 3 diastereoisomers of **23**: ^{1}H NMR (500 MHz, $CDCl_3$, mixture of 3 diastereoisomers) δ 5.76 (s), 5.75 (s), 5.50 (s), 5.37 (s) (1H, H-4), 4.73 (d, $J_{CHOMOM,9'}$ = 7.4 Hz), 4.65 (d, $J_{CHOMOM,9'}$ = 6.8 Hz), 4.33 (d, $J_{CHOMOM,9'}$ = 10.0 Hz), 4.26 (d, $J_{CHOMOM,9'}$ = 10.0 Hz) (1H, C*H*OMOM), 4.60 (s), 4.59 (s), 4.58 (s) (2H, OCH_2), 4.05 (m, 1H, H-9a'), 3.87 (m, 1H, H-3'), 3.35 (s), 3.32 (s), 3.29 (s), 3.28 (s) (3H, OCH_3), 3.22 (m, 1H, H-3'), 2.55 (m, 1H, H-6'), 2.47 (m, 2H, H-6', H-1'), 2.32 (m, 1H, H-9'), 2.17 (m, 1H, H-1'), 1.89 (m, 1H, H-2'), 1.60 (m, 5H, 2H-7', 2H-8', H-2'), 1.34 (s), 1.30 (s), 1.23 (s), 1.21 (s) (3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$, mixture of 3 diastereoisomers) δ 178.0 (CO), 177.8 (CO), 174.0 (CO), 173.6 (CO), 152.7, 152.6 (C-5), 111.0, 110.9 (C-4), 95.9, 95.6 (OCH_2), 74.3, 74.0, 72.8 (*C*HOMOM), 61.1 (C-9a'), 56.2, 56.0 (OCH_3), 52.6, 52.5, 51.7 (C-3), 47.5 (C-3'), 40.7, 40.2 (C-9'), 37.9 (C-6'), 32.8, 32.5 (C-8'), 31.9 (C-1'), 23.4 (C-2'), 19.1 (C-7'), 18.9, 18.8 (CH_3). MS *m/z* (ESI+, MeOH): 667 (MNa^+).

*4.16. (6S,7R,8S)-6-Hydroxymethyl-8-triisopropylsilyloxy-1-azabicyclo[5.3.0]decane (**24**)*

To a solution of ester **1** (265 mg, 0.69 mmol) in anhydrous toluene (30 mL) under nitrogen atmosphere, DIBAL-H (1M in toluene, 4.2 mL, 4.2 mmol) was added dropwise at –78 °C and the mixture was stirred at this temperature for 3 h. When TLC analysis (hexanes/EtOAc, 7:3) showed total consumption of **1**, H_2O (3 mL) was added and the mixture was allowed to warm to room temperature. Then, it was washed with a saturated aqueous solution of sodium tartrate (4 mL) and the aqueous phase was extracted with CH_2Cl_2 (3x4 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The remaining oil was purified by column chromatography on neutral alumina (hexanes/EtOAc, from 1:1 to 3:7) to yield aminoalcohol **24** as a syrup (160 mg, 0.47 mmol, 68%): R_f 0.44 (hexanes/EtOAc, 7:3); ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.29 (d, $J_{8,9}$ = 4.7 Hz, 1H, H-8), 3.91 (dd, $J_{1',1'}$ = 10.9 Hz, $J_{1',6}$ = 1.8 Hz, 1H, H-1'), 3.50 (dt, $J_{1',1'}$ = 10.9 Hz, $J_{1',6}$ = 2.1 Hz, 1H, H-1'), 3.04 (m, 2H, H-2, H-10), 2.95 (bs, 1H, H-7), 2.69 (ddd, $J_{10,10}$ = 12.7 Hz, $J_{10,9}$ = 8.7 Hz, $J_{10,9}$ = 5.2 Hz, 1H, H-10), 2.24 (ddd, $J_{2,2}$ =11.7 Hz, $J_{2,3}$ = 9.3 Hz, $J_{2,3}$ = 4.5 Hz, 1H, H-2), 1,79 (m, 9H, 2H-3, 2H-4, 2H-5, H-6, 2H-9), 1.07 (bs, 21H, 3 Si*CH*CH_3, 18 SiCH*CH*$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 77.9 (C-8), 76.9 (C-7), 66.29 (C-1'), 56.4 (C-2), 54.9 (C-10), 37.6 (C-6), 35.4 (C-9), 31.1 (C-5), 30.5 (C-3), 25.0 (C-4), 18.0 (SiCH*CH*$_3$), 12.17 (Si*CH*CH_3); HRMS (ESI+) calcd for [$C_{19}H_{39}NO_2SiH^+$]: 342.2823, found: 342.2819.

*4.17. (6S,7R,8S)-8-Triisopropylsilyloxy-1-azabicyclo[5.3.0]decane-6-carbaldehyde (**25**)*

A solution of DMSO (46 µL, 647 µmol) in dry CH_2Cl_2 (113 µL) was added to a stirred solution of oxalyl chloride (2M in CH_2Cl_2, 176 µL, 351 µmol) at –78 °C under nitrogen atmosphere and the mixture was stirred at this temperature for 30 min. Next, a solution of **24** (100 mg, 293 µmol) in dry CH_2Cl_2 (321 µL) was added and the mixture was stirred for 3 h. Then, Et_3N (500 µL) was added, the mixture was washed with H_2O (2 mL), and the aqueous layer was extracted with CH_2Cl_2 (3x2 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum, affording aldehyde **25** (93 mg, 274 µmol, 94%) which was immediately submitted to the next transformation without further purification: R_f 0.42 (CH_2Cl_2/Et_2O, 4:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.74 (d, $J_{1',6}$ = 2.2 Hz, 1H, CHO), 4.43 (m, 1H, H-8), 3.01 (m, 2H, H-2, H-10), 2.84 (bs, 1H, H-7), 2.66 (m, 2H, H-6, H-10), 2.31 (m, 1H, H-2), 2.20 - 1.52 (m, 8H, 2H-3, 2H-4, 2H-5, 2H-9), 1.05 (bs, 21H, 3 Si*CH*CH_3, 18 SiCH*CH*$_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 205.7 (C-1'), 78.1 (C-8), 74.5 (C-7), 56.5 (C-2), 55.1 (C-10), 51.9 (C-6), 35.1 (C-9), 29.3 (C-5), 26.6 (C-3), 24.0 (C-4), 18.0 (SiCH*CH*$_3$), 12.2, (Si*CH*CH_3).

*4.18. (6S,7R,8S)-6-{(1S)-Hydroxy-(2R)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl]methyl}-8-triisopropylsilyloxy-1-azabicyclo[5.3.0]decane (**26**)*

BuLi (1.6M in hexanes, 188 µL, 301 µmol) was added to a solution of diisopropylamine (47 µL, 301 µmol) in dry THF (1.4 mL) at –78 °C under nitrogen atmosphere, and the mixture was stirred for 30 min. A solution of furanone **2** (26 µL, 301 µmol) in dry THF (3.6 mL) was added over the freshly prepared LDA solution and the mixture was stirred at –78 °C for 5 min. Then, a solution of aldehyde **25** (93 mg, 274 µmol) in dry THF (1.4 mL) was added and the mixture was stirred for 1 h at –78 °C. The reaction mixture was treated with saturated aqueous NH_4Cl (3 mL) and the aqueous phase was extracted with EtOAc (2x5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography on neutral alumina (CH_2Cl_2/Et_2O, 4:1) to furnish compound **26** as a pale yellow liquid (93 mg, 212 µmol, 78%): R_f 0.14 (CH_2Cl_2/Et_2O, 4:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34 (m, 1H, H-3'), 4.69 (m, 1H, H-2'), 4.57 (m, 1H, H-8), 3.44 (dd, $J_{1',2'}$ = 9.2 Hz, $J_{1',6}$ = 2.2 Hz, 1H, H-1'), 3.17 - 2.96 (m, 3H, H-7, H-10, OH), 2.70 (ddd, $J_{10,10}$ = 12.2 Hz, $J_{10,9}$ = 9.0 Hz, $J_{10,9}$ = 5.8 Hz, 1H, H-10), 2.36 (m, 3H, $2H_2$, H-6), 2.15 (tdd, $J_{9,9}$ = 12.4 Hz, $J_{9,10}$ = 6.7 Hz, $J_{9,10}$ = $J_{9,8}$ = 5.8 Hz, 1H, H-9), 1.91 (t, $J_{Me\text{-}3'}$ = 1.6 Hz, 3H, CH_3), 1.95 - 1.65 (m, 10H, 2H-3, 2H-4, 2H-5, H-9, 3Si*CH*CH_3), 1.05 (bs, 18H, 3SiCH*CH*$_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.4 (C-5'), 149.4 (C-3'); 129.9 (C-4'), 83.0 (C-2'), 81.3 (C-1'), 78.0 (C-8), 77.4 (C-7), 55.7 (C-2), 54.9 (C-10), 36.8 (C-6), 35.6, 34.9, 28.8, 24.7 (C-3/C-4/C-5/C-9), 18.2 (SiCH*CH*$_3$), 12.34 (Si*CH*CH_3), 10.80 (CH_3); HRMS (ESI+) calcd for [$C_{24}H_{43}NO_4SiH^+$]: 438.3040, found: 438.3029. The relative configuration of **26** was assumed to be the same as that of the analogous lactam **9**.

*4.19. (6S,7R,8S)-8-Hydroxy-6-{(1S)-(methoxymethoxy)-[(2R)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl]methyl}-1-azabicyclo[5.3.0]decane (**27**)*

Dimethoxymethane (120 µL, 1346 µmol) and PTSA (21 mg, 112 µmol) were added to a solution of **26** (43 mg, 98 µmol) in dry CH_2Cl_2 (1 mL) at room temperature. A Dean-Stark apparatus with molecular sieves (4Å) was connected to the system and the reaction mixture was heated at the reflux temperature and stirred overnight. Next, saturated aqueous Na_2CO_3 (300 µL) was added to the reaction mixture and the aqueous phase was extracted with CH_2Cl_2 (4x500 µL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography on neutral alumina (EtOAc/30% aqueous NH_3, 95:5) to furnish aminoalcohol **27** as a pale yellow liquid (13 mg, 40 µmol, 40%): R_f 0.14 (EtOAc/30% aqueous NH_3, 95:5); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34 (m, 1H, H-3'), 4.83 (m, 1H, H-2'), 4.68 (m, 2H, O*CH*$_2$O), 4.40 (ddd, $J_{8,9}$ = 6.1 Hz, $J_{8,9}$ = 3.9 Hz, $J_{8,7}$ = 1.9 Hz, 1H, H-8), 3.59 (dd, $J_{1',2'}$ = 8.3 Hz, $J_{1',7}$ = 3.5 Hz, 1H, H-1'), 3.40 (s, 3H, CH_3O), 3.12 (m, 2H, H-10, OH), 2.97 (bdd, $J_{7,1'}$ = 3.9 Hz, $J_{7,6}$ = 1.3 Hz, 1H, H-7), 2.61 (ddd, $J_{10,10}$ = 11.2 Hz, $J_{10,9}$ = 9.5 Hz, $J_{10,9}$ = 7.0 Hz, 1H, H-10), 2.40 (m, 3H, 2H-2, H-6), 2.15 (dddd, $J_{9,9}$ = 13.7 Hz, $J_{9,10}$ = 11.3 Hz, $J_{9,10}$ = $J_{9,8}$ = 7.0 Hz, 1H, H-9), 1.95 (t, $J_{Me\text{-}3'}$ = 1.7 Hz, 3H, CH_3), 1.78 (m, 7H, 2H-3, 2H-4, 2H-5, H-9); HRMS (ESI+) calcd for [$C_{17}H_{27}NO_5H^+$]: 326.1967, found: 326.1958.

4.20. *Methyl (6S,7R,8S)-2-oxo-8-hydroxy-1-azabicyclo[5.3.0]decane-6-carboxylate (**28**)*

To a solution of ester **1** (200 mg, 520 µmol) in anhydrous THF (9.4 mL) under nitrogen atmosphere, was added $3HF{\cdot}Et_3N$ (1.7 mL, 10.43 mmol) and the mixture was heated at the reflux temperature under stirring for 3 h. Then, the organic solvent was removed under vacuum and the resultant oil was solved in CH_2Cl_2 (6 mL) and washed with saturated aqueous NH_4Cl (4 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (from EtOAc to EtOAc/MeOH, 10:1) to afford alcohol **28** as a yellowish syrup (62.5 mg, 280 µmol, 53%): R_f 0.18 (EtOAc/MeOH, 10:1); IR (ATR) 3439, 2953, 1729, 1618, 1464, 1159, 1036 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.52 (ddd, $J_{8,9}$ = $J_{8,7}$ = 5.0 Hz, 1H, H-8), 3.81 (ddd, $J_{10,10}$ = 15.0 Hz, $J_{10,9}$ = 7.5 Hz, $J_{10,9}$ = 5.0 Hz 1H, H-10), 3.72 (bd, $J_{7,8}$ = 5.0 Hz, 1H, H-7), 3.64 (s, 3H, CH_3), 3.36 (ddd, $J_{10,10}$ = 15.0 Hz, $J_{10,9}$ = $J_{10,9}$ = 7.5 Hz, 1H, H-10), 3.07 (bt, $J_{6,5}$ = 3.6 Hz, 1H, H-6), 2.63 - 2.28 (m, 3H, H-5, 2H-3), 2.08 (m, 1H, H-9), 1.73 (m, 4H, H-9, H-5, 2H-4); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.5 (C-2), 172.2 (*C*O_2Me), 76.6 (C-8), 67.3 (C-7), 51.7 (CH_3), 45.2 (C-10), 43.7 (C-6), 37.7 (C-3), 32.5 (C-5), 32.1 (C-9), 19.7 (C-4); HRMS (ESI+) calcd for $[C_{11}H_{17}NO_4Na^+]$: 250.1050, found: 250.1044.

4.21. *(4R,7S,12R)-5-Oxa-1-azatricyclo[5.4.1.0^{4,12}]dodecane-6,11-dione, (**30**)*

PPh_3 (276 mg, 1.05 mmol) was added to a solution of alcohol **28** (77 mg, 0.34 mmol) and CBr_4 (343 mg, 1.04 mmol) in anhydrous CH_2Cl_2 (670 µL) under nitrogen atmosphere at 0 °C and the mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with EtOH (60 µL) and stirred for 30 min. Then, Et_2O (670 µL) was added to favour the precipitation of Ph_3PO. The mixture was filtered through a short pad of Celite®, the organic solvent was removed under reduced pressure and the resultant precipitate was purified by column chromatography (from hexanes/EtOAc, 1:1, to EtOAc/MeOH, 9:1) to furnish a white solid which was identified as lactone **30** (20 mg, 0.10 mmol, 30%): R_f 0.18 (EtOAc/MeOH, 9:1); IR (ATR) 2954, 2861, 1762, 1641, 1423, 1185, 1163, 994 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.13 (t, $J_{4,12} \approx J_{4,3} \approx$ 5.0 Hz, 1H, H-4), 4.58 (dd, $J_{12,7}$ = 7.2 Hz, $J_{12,4}$ = 5.4 Hz, 1H, H-12), 3.93 (ddd, $J_{2,2}$ = 11.7 Hz, $J_{2,3}$ = 9.0 Hz, $J_{2,3}$ = 1.4 Hz, 1H, H-2), 3.34 (dt, $J_{2,2}$ = 11.7 Hz, $J_{2,3}$ = 6.6 Hz, 1H, H-2), 2.77 (ddd, $J_{7,8}$ = 11.5 Hz, $J_{7,12}$ = 7.2 Hz, $J_{7,8}$ = 5.2 Hz, 1H, H-7), 2.50 (m, 2H, 2H-10), 2.36 (m, 1H, H-3), 2.23 (m, 1H, H-8), 2.10 (dddd, $J_{3,3}$ = 14.0 Hz, $J_{3,2}$ = 11.3 Hz, $J_{3,2}$ = 9.0 Hz, $J_{3,4}$ = 4.9 Hz, 1H, H-3), 1.92 (m, 1H, H-9), 1.70 (m, 1H, H-9), 1.51 (dddd, $J_{8,8}$ = 14.4 Hz, $J_{8,9}$ = 12.5 Hz, $J_{8,9}$ = 11.6 Hz, $J_{8,7}$ = 4.7 Hz, 1H, H-8); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 176.7 (C-6), 171.0 (C-11), 82.4 (C-4), 60.5 (C-12), 43.4 (C-2), 42.1 (C-7), 33.7 (C-10), 29.7 (C-3), 24.5 (C-8), 18.8 (C-9); HRMS (ESI+) calcd for $[C_{10}H_{13}NO_3Na^+]$: 218.0793, found: 218.0790.

4.22. *(E)-3-{(6R,7R,8S)-2-Oxo-8-triisopropylsilyloxy-1-azabicyclo[5.3.0]decan-6-yl}acrylate (**31**)*

Methyl (triphenylphosphanyl)acetate (2.4 g, 7.2 mmol) was added to a solution of aldehyde **7** (853 mg, 2.4 mmol) in EtOAc (54 mL) at room temperature and the resulting mixture was heated at 75 °C under stirring overnight. After cooling the reaction mixture, it was washed with saturated aqueous NH_4Cl (20 mL), and the aqueous layer was extracted with EtOAc (2x20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The resultant oil was purified by column chromatography (hexanes/EtOAc, 1:1) to furnish ester **31** as a white solid (860 mg, 2.1 mmol, 87%): R_f 0.48 (EtOAc); IR (ATR) 2942, 2865, 1721, 1605, 1433, 1241, 1157, 988, 803 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.90 (dd, $J_{1',2'}$ = 15.7 Hz, $J_{1',6}$ = 9.8 Hz, 1H, H-1'), 5.87 (d, $J_{2',1'}$ = 15.5 Hz, 1H, H-2'), 4.10 (m, 1H, H-8), 3.74 (m, 2H, H-7,H-10), 3.69 (s, 3H, OCH_3), 3.37 (ddd, $J_{10,10}$ = 18.7 Hz, $J_{10,9}$ = 7.5 Hz, $J_{10,9}$ = 7.5 Hz, 1H, H-10), 2.73 (m, 1H, H-6), 2.50 (m, 2H, 2H-3), 1.79 (m, 6H, 2H-4, 2H-5, 2H-9), 1.04 (bs, 21H, 3 Si*CH*CH_3, 18 SiCH*CH*$_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.0 (C-2), 166.5 (C-3'), 146.7 (C-1'), 124.2 (C-2'), 78.4 (C-8), 70.1 (C-7), 52.2 (CH_3), 45.5 (C-10), 42.8 (C-6), 38.4 (C-3), 37.3 (C-9), 32.9 (C-5), 18.4 (C-4), 17.7 (Si*CH*CH_3), 11.9 (SiCH*CH*$_3$); HRMS (ESI+) *c*alcd for $[C_{22}H_{39}NO_4SiNa^+]$: 432.2541, found: 432.2538.

4.23. *(E)-3-{(6R,7R,8S)-2-Oxo-8-hydroxy-1-azabicyclo[5.3.0]decan-6-yl}acrylate (**32**)*

$3HF{\cdot}Et_3N$ (4.0 mL, 24.4 mmol) was added to a solution of ester **31** (500 mg, 1.2 mmol) in anhydrous THF (25 mL) under nitrogen atmosphere at room temperature and the mixture was heated at the reflux temperature under stirring for 3h. Then, the organic solvent was removed under vacuum and the residue was solved in CH_2Cl_2 (15 mL) and washed with saturated aqueous NH_4Cl (8 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resultant oil was purified by column chromatography (EtOAc to EtOAc/MeOH, 9:1) to furnish alcohol **32** as a white solid (300 mg, 1.2 mmol, 97%): R_f 0.23 (EtOAc/MeOH, 9:1); IR (ATR) 3345, 2932, 1715, 1618, 1464, 1159, 1036 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.87 (dd, $J_{1',2'}$ = 14.2 Hz, $J_{1',6}$ = 8.3 Hz, 1H, H-1'), 5.90 (d, $J_{2',1'}$ = 15.2 Hz 1H, H-2'), 4.05 (m, 1H, H-8), 3.78 (m, 2H, H-7, H-10), 3.68 (s, 3H, OCH_3), 3.33 (ddd, $J_{10,10}$ = 18.7 Hz, $J_{10,9}$ = 7.5 Hz, $J_{10,9}$ = 7.5 Hz, 1H, H-10), 2.82 (m, 1H, H-6), 2.50 (m, 2H, 2H-3), 1.92 (m, 3H, 2H-5, H-9), 1.71 (m, 3H, 2H-4, H-9); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.0 (C-2), 166.2 (C-3'), 145.9 (C-1'), 124.0 (C-2'), 76.3 (C-8), 68.5 (C-7), 51.6 (CH_3), 45.1 (C-10), 42.1 (C-6), 37.8 (C-3), 36.3 (C-9), 31.7 (C-5), 18.4 (C-4); HRMS (ESI+) calcd for $[C_{13}H_{19}NO_4Na^+]$: 276.1206, found: 276.1197.

4.24. *Bis{9-[(E)-3-methoxy-3-oxoprop-1-en-1-yl]-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-1-yl} oxalate (**34**)*

Anhydrous DMF (44 µL) and oxalyl bromide (19 µL, 205 mmol) were added to a solution of alcohol **32** (43 mg, 170 µmol) in anhydrous CH_2Cl_2 (1 mL) at 0 °C under nitrogen atmosphere, and the mixture was allowed to warm up to room temperature and stirred for 1 h. After that time, the mixture was washed with saturated aqueous $NaHCO_3$ (1 mL) and the aqueous layer was extracted with CH_2Cl_2 (3x0.5 mL). Then, the combined organic extracts were washed with brine (2 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual yellowish oil was identified as compound **34** (20 mg, 34 µmol, 42%): R_f 0.41 (EtOAc/MeOH, 9:1); IR (ATR) 2928, 2855, 1719, 1635, 1536, 1162 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.91 (dd, $J_{1',2'}$ = 15.7 Hz, $J_{1',6}$ = 10.2 Hz, 1H, H-1'), 5.97 (d, $J_{2',1'}$ = 15.7 Hz, 1H, H-2'), 5.09 (m, 1H, H-8), 4.07 (bs, 1H, H-7), 3.72 (s, 3H, CH_3), 3.65 (dd, $J_{10,9}$ = 8.4 Hz, $J_{10,9}$ = 4.1 Hz, 2H, 2H-10), 2.87 (m, 1H, H-6), 2.53 (m, 2H, 2H-3), 1.95 (m, 6H, 2H-4, 2H-5, 2H-9); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.6 (C-2), 165.9 (*C*O_2Me), 156.9 (O_2C-*C*O_2), 144.5 (C-1'), 124.6 (C-2'), 83.0 (C-8), 66.4 (C-7), 51.8 (CH_3), 45.4 (C-10), 42.7 (C-6), 38.0 (C-3), 36.3 (C-9), 29.7/18.5 (C-4/C-5); HRMS (ESI+) calcd for $[C_{28}H_{36}N_2O_{10}Na^+]$: 583.2268, found: 583.2107. Attempted purification of **34** by column chromatography (from hexanes/EtOAc, 4:1, to EtOAc/MeOH, 9:1) led to hydrolysis, furnishing the starting alcohol **32**.

4.25. *(E)-3-{(6R,7R,8S)-2-oxo-8-triisopropylsilyloxy-1-azabicyclo[5.3.0]decan-6-yl}-2-propen-1-ol (**35**) and (E)-3-*

*{(6R,7R,8S)-8-triisopropylsilyloxy-1-azabicyclo[5.3.0]decan-6-yl}-2-propen-1-ol (**36**)*

DIBAL-H (1M in toluene, 8.9 mL, 8.90 mmol) was added to a solution of ester **31** (912 mg, 2.22 mmol) in anhydrous CH_2Cl_2 (20 mL) at –78 °C under nitrogen atmosphere and the resulting mixture was stirred for 4 h. Then, the reaction mixture was quenched with MeOH (25 mL) and filtered through Celite®. The organic solvents were removed under reduced pressure affording a crystaline solid, which purification by column chromatography (from hexanes/EtOAc, 1:1, to EtOAc/MeOH, 9:1) furnished hydroxylactam **35** as a white solid (200 mg, 0.52 mmol, 24%) and aminoalcohol **36** as a white solid (405 mg, 1.10 mmol, 50%). **35:** R_f 0.16 (EtOAc/MeOH,10:1); IR (ATR) 3367, 2940, 2865, 2360, 1623, 1460, 1381, 882 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.73 (m, 2H, $H_{1'}$, $H_{2'}$), 4.20 (dd, $J_{8,9}$ = 8.2 Hz, $J_{8,9}$ = 4.8 Hz, 1H, H-8), 4.12 (d, $J_{3',2'}$ = 4.6 Hz, 2H, 2H-3'), 3.75 (m, 2H, H-7, H-10), 3.36 (ddd, $J_{10,10}$ = 11.6 Hz, $J_{10,9}$ = 6.9 Hz, $J_{10,9}$ = 5.3 Hz, 1H, H-10), 2.55 (m, 3H, 2H-3, H-6), 1.99 (m, 3H, 2H-5, H-9), 1.77 (m, 3H, 2H-4, H-9), 1.06 (bs, 21H, TIPS); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 174.1 (C-2), 132.8 (C-1'), 128.8 (C-2'), 78.0 (C-8), 70.4 (C-7), 63.3 (C-3'), 45.3 (C-10), 42.5 (C-6), 38.1 (C-3), 37.5 (C-9), 32.7 (C-5), 18.6 (C-4), 18.1 (SiCH*CH*$_3$), 12.3 (Si*CH*CH$_3$); HRMS (ESI+) calcd for $[C_{21}H_{39}NO_3SiNa^+]$: 404.2597, found: 404.2592. **36:** R_f 0.14 (EtOAc); IR (ATR) 3341, 2926, 2864, 2360, 1627, 1462, 1386, 1047 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.83 (dd, $J_{1',2'}$ = 15.5 Hz, $J_{1',6}$ = 9.0 Hz, 1H, H-1'); 5.63 (dt, $J_{2',1'}$ = 15.5 Hz, $J_{2',3'}$ = 5.5 Hz, 1H, H-2'); 4.15 (m, 3H, 2H-3', H-8), 3.15 (m, 2H, H-2, H-10), 2.80 (bd, $J_{7,6}$ = 5.3 Hz, 1H, H-7), 2.74 (m, 1H, H-10), 2.49 (m, 2H, H-2, H-6), 1.66 (m, 8H, 2H-3, 2H-4, 2H-5, 2H-9), 1.05 (bs, 21H, TIPS); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 133.7 (C-1'), 130.5 (C-2'), 77.3/77.2 (C-7/C-8), 63.6 (C-3'), 56.7 (C.10), 55.3 (C-2), 43.3 (C-6), 34.7/34.1/30.2/23.1 (C-3/C-9/C-5/C-4), 18.2 (SiCH*CH*$_3$), 12.3 (Si*CH*CH$_3$); HRMS (ESI+) calcd for $[C_{21}H_{41}NO_2SiH^+]$: 368.2985, found: 368.2981.

*4.26. (E)-3-{(6R,7R,8S)-2-Oxo-8-triisopropylsilyloxy-1-azabicyclo[5.3.0]decan-6-yl}-2-propenal (**37**)*

DMPI (395 µL, 15% wt in CH_2Cl_2) was added to a solution of alcohol **35** (54 mg, 141 µmol) in anhydrous CH_2Cl_2 (2.8 mL) at room temperature under nitrogen atmosphere and the mixture was stirred at this temperature for 2 h. After this time, the mixture was quenched with 200 µL of a solution prepared by addition of $Na_2S_2O_3$ (17 g) to saturated aqueous $NaHCO_3$ (90 mL), and the resulting mixture was stirred for 15 min. Then, the aqueous phase was extracted with CH_2Cl_2 (2x2 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 1:1) affording aldehyde **37** as a colourless syrup (36 mg, 95 µmol, 68%): R_f 0.40 (EtOAc); $[\alpha]_D$ +16 (*c* 1.66, $CHCl_3$); IR(ATR) 2925, 2864, 2360, 2341, 1734, 1687, 1672, 1637, 1455, 1425, 1382, 1365, 1208, 1185, 1032, 881 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.53 (d, $J_{3',2'}$ = 7.7 Hz, 1H, H-3'), 6.84 (dd, $J_{1',2'}$ = 15.8 Hz, $J_{1',6}$ = 9.6 Hz, 1H, H-1'), 6.22 (dd, $J_{2',1'}$ = 15.6 Hz, $J_{2',3'}$ = 7.6 Hz, 1H, H-2'), 4.17 (dd, $J_{8,9}$ = 9.0, $J_{8,9}$ = 5.3 Hz, 1H, H-8), 3.86 (m, 2H, H-7, H-10), 3.39 (dt, $J_{10,10}$ = 12.0, $J_{10,9}$ = 7.0 Hz, 1H, H-10), 2.95 (d, $J_{6,11}$ = 9.6 Hz, 1H, H-6), 2.59 (m, 2H, 2H-3), 1.89 (m, 6H, 2H-4, 2H-5, 2H-9), 1.07 (bs, 21H, TIPS); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 193.3 (C-3'), 173.8 (C-2), 154.8 (C-1'), 135.4 (C-2'), 78.0 (C-8), 69.7 (C-7), 45.3 (C-10), 42.3 (C-6), 38.1/37.0/32.7/29.8 (C-3/C-4/C-5/C-9); 18.1 (SiCH*CH*$_3$); 12.3 (Si*CH*CH$_3$); HRMS (ESI+) calcd for $[C_{21}H_{37}NO_3SiNa^+]$: 402.2435, found: 402.2428. Aldehyde **37** epimerizes rapidly and it was immediately submitted to the next synthetic transformation.

*4.27. (E)-3-{(6R,7R,8S)-8-Triisopropylsilyloxy-1-azabicyclo[5.3.0]decan-6-yl}-2-propenal (**38**)*

DMPI (440 µL, 15% wt in CH_2Cl_2) was added to a solution of alcohol **36** (61 mg, 166 µmol) in anhydrous CH_2Cl_2 (3 mL) at room temperature under nitrogen atmosphere and the mixture was stirred at this temperature for 2 h. After this time, the mixture was quenched with 200 µL of a solution prepared by addition of $Na_2S_2O_3$ (17 g) to a saturated aqueous solution of $NaHCO_3$ (90 mL), and the mixture was stirred for 15 min. Then, the aqueous phase was extracted with CH_2Cl_2 (2x2 mL), the combined organic extracts were dried with anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 1:1) affording aldehyde **38** as a colorless syrup (35 mg, 96 µmol, 57%): R_f 0.36 (EtOAc); $[\alpha]_D$ +70 (*c* 1.14, $CHCl_3$); IR(ATR) 2925, 2864, 2805, 2360, 2341, 1692, 1461, 1109, 1045, 882 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.53 (d, $J_{3',2'}$ = 7.9 Hz, 1H, H-3'), 7.05 (dd, $J_{1',2'}$ = 15.7 Hz, $J_{1',6}$ = 9.4 Hz, 1H, H-1'), 6.10 (dd, $J_{2',1'}$ = 15.7 Hz, $J_{2',3'}$ = 7.9 Hz, 1H, H-2'), 4.00 (bs, 1H, H-8), 3.04 (m, 2H, H-2, H-10), 2.83 (s, 1H, H-7), 2.75 (m, 2H, H-6, H-10), 2.45 (m, 1H, H-2), 1.72 (m, 8H, 2H-3, 2H-4, 2H-5, 2H-9), 1.06 (bs, 21H, TIPS); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 194.3 (C-3'), 161.4 (C-1'), 132.7 (C-2'), 77.7 (C-8), 76.0 (C-7), 56.0 (C-10), 54.9 (C-2), 44.4 (C-6), 34.8/33.9/30.6/22.9 (C-3/C-4/C-5/C-9), 18.1 (SiCH*CH*$_3$), 12.1 (Si*CH*CH$_3$); HRMS (ESI+) calcd for $[C_{21}H_{39}NO_2SiH^+]$: 366.2823, found: 366.2820. Aldehyde **38** epimerizes rapidly and it was immediately submitted to the next synthetic transformation.

*4.28. (2R,3S)- (trans-**47**) and (2S,3S)-2-Ethoxy-5-oxo-1-[(E)-6-oxohex-4-enyl]pyrrolidin-3-yl acetate (cis-**47**)*

1-Penten-3-one (193 µL, 1.95 mmol) and a solution of HG-II catalyst (12 mg, 0.02 mmol) in dry and degassed CH_2Cl_2 (280 µL) under nitrogen atmosphere were added to a solution of aminal **44** (166 mg, 0.65 mmol) in dry and degassed CH_2Cl_2 (2.2 mL) at room temperature under nitrogen atmosphere. The resulting green solution was stirred for 1 h at room temperature. Then, an additional portion of catalyst (12 mg, 0.02 mmol, 3 mol%) was added to the brown solution and the mixture was stirred for 1 h more. After this time, TLC analysis of the reaction mixture (EtOAc) did not show starting aminal **44**. The reaction mixture was filtered through silica gel, washing with EtOAc. The organic solvent was evaporated under vacuum and the remaining brown oil was purified by column chromatography (hexanes/EtOAc, 1:1) to afford a mixture of diastereoisomers (6:1) of ketone **47** as a pale yellow oil (157 mg, 0.50 mmol, 78%): HRMS (ESI+) calcd for $[C_{16}H_{25}NO_5Na^+]$: 334.1625, found: 334.1627. Analytical samples of *trans*- and *cis*-**47** could be isolated by repeated column chromatography. *trans*-**47**: R_f 0.44 (EtOAc); $[\alpha]_D$ –40 (*c* 1.01, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 6.80 (dt, $J_{4',5'}$ = 15.9 Hz, $J_{4',3'}$ = 6.8 Hz, 1H, H-4'), 6.11 (dt, $J_{5',4'}$ = 15.9 Hz, $J_{5',3'}$ = 1.5 Hz, 1H, H-5'), 5.05 (d, $J_{3,4}$ = 6.4 Hz, 1H, H-3), 4.66 (s, 1H, H-2), 3.72 (dq, $J_{1'',1''}$ = 9.3 Hz, $J_{1'',2''}$ = 7.0 Hz, 1H, H-1''), 3.56 (dq, $J_{1'',1''}$ = 9.3 Hz, $J_{1'',2''}$ = 7.0 Hz, 1H, H-1''), 3.43 (ddd, $J_{1',1'}$ = 14.0 Hz, $J_{1',2'} \approx J_{1',2'}$ = 7.2 Hz, 1H, H-1'), 3.22 (ddd, $J_{1',1'}$ = 14.0 Hz, $J_{1',2'} \approx J_{1',2'}$ = 7.2 Hz, 1H, H-1'), 2.87 (dd, $J_{4,4}$ = 17.9 Hz, $J_{4,3}$ = 6.4 Hz, 1H, H-4), 2.54 (q, $J_{7',8'}$ = 7.3 Hz, 2H, 2H-7'), 2.32 (d, $J_{4,4}$ = 17.9 Hz, 1H, H-4), 2.24 (ddd, $J_{3',2'}$ = 14.2 Hz, $J_{3',4'}$ = 6.7 Hz, $J_{3',2'}$ = 1.4 Hz, 2H, 2H-3'), 2.07 (s, 3H, CH_3CO), 1.73 (ddd, $J_{2',3'}$ = 14.2 Hz, $J_{2',1'}$ = 7.4 Hz, $J_{2',3'}$ = 1.4 Hz, 2H, 2H-2'), 1.22 (t, $J_{2'',1''}$ = 7.0 Hz, 3H, 3H-2''), 1.08 (t, $J_{8',7'}$ = 7.3 Hz, 3H, 3H-8'); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 200.9 (C-6), 172.6 (C-5), 170.2 (CH$_3$*CO*), 145.2 (C-4'), 130.4 (C-3'), 93.2 (C-2), 70.4 (C-3), 63.7 (C-1''), 40.2 (C-1'), 35.7 (C-4), 33.4 (C-7'), 29.6 (C-3'), 26.3 (C-2'), 20.9 (*CH*$_3$CO), 15.2 (C-2''), 8.0 (C-8'). *cis*-**47**: R_f 0.44 (EtOAc); ^1H NMR (250 MHz, $CDCl_3$) δ 6.79 (dt, $J_{4',5'}$ = 15.8 Hz, $J_{4',3'}$ = 6.8 Hz, 1H, H-4'), 6.12

(dt, $J_{5',4'}$ = 15.9 Hz, $J_{5',3'}$ = 1.4 Hz, 1H, H-5'), 5.16 (td, $J_{3,4}$ = 8.1 Hz, $J_{3,4}$ = 5.3 Hz, 1H, H-3), 5.00 (d, $J_{2,3}$ = 5.3 Hz, 1H, H-2), 3.54 (m, 3H, 2H-1'', H-1'), 3.16 (ddd, $J_{1',1'}$ = 14.0 Hz, $J_{1',2'}$ = 7.9 Hz, $J_{1',2'}$ = 6.2 Hz, 1H, H-1'), 2.62 (dd, $J_{4,3}$ = 8.1 Hz, $J_{4,4}$ = 1.3 Hz, 1H, H-4), 2.54 (q, $J_{7',8'}$ = 7.3 Hz, 2H, 2H-7'), 2.22 (m, 2H, 2H-3'), 2.11 (s, 3H, CH_3CO), 1.73 (m, 2H, 2H-2'), 1.18 (t, $J_{2'',1''}$ = 7.0 Hz, 3H, 3H-2''), 1.08 (t, $J_{8',7'}$ = 7.3 Hz, 3H, 3H-8'); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 201.0 (C-6), 171.1 (C-5), 170.8 (CH_3CO), 145.2 (C-4'), 130.5 (C-3'), 88.4 (C-2), 67.9 (C-3), 65.6 (C-1''), 40.4 (C-1'), 34.6 (C-4), 33.6 (C-7'), 29.8 (C-3'), 26.4 (C-2'), 20.8 (CH_3CO), 15.6 (C-2''), 8.2 (C-8').

*4.29. (1S,9aR)-3-Oxo-9-propionyl-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-1-yl acetate (**48**)*

Me_2S (12 µL, 160 µmol) and TMSOTf (48 µL, 267 µmol) were added to a mixture of diastereoisomers of ketone **47** (33 mg, 107 µmol) in CH_3CN (600 µL) at –35 °C. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. Then, the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL). After evaporation of the acetonitrile under vacuum, the whole mixture was extracted with CH_2Cl_2 (3x1 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (EtOAc) afforded starting **47** (10 mg, 32 µmol, 30%) and bicycle **48** as colourless oil (12 mg, 45 µmol, 41%): R_f 0.28 (EtOAc); $[\alpha]_D$ –71 (*c* 0.31, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.04 (ddd, $J_{8,7}$ = 9.0 Hz, $J_{8,7}$ = 5.1 Hz, $J_{8,9a}$ = 0.8 Hz, 1H, H-8), 5.09 (ddd, $J_{1,2}$ = 7.0 Hz, $J_{1,2}$ = $J_{1,9a}$ = 2.9 Hz, 1H, H-1), 4.77 (td, $J_{9a,1}$ = 2.4 Hz, $J_{9a,8}$ = 1.3 Hz, 1H, H-9a), 4.18 (ddd, $J_{5,5}$ = 14.1 Hz, $J_{5,6}$ = 8.8 Hz, $J_{5,6}$ = 5.4 Hz, 1H, H-5), 2.92 (ddd, $J_{5,5}$ = 14.4 Hz, $J_{5,6}$ = 7.8 Hz, $J_{5,6}$ = 6.6 Hz, 1H, H-5), 2.68 (m, 3H, H-2, 2H-2'), 2.30 (m, 4H, H-2, H-6, 2H-7), 2.08 (s, 3H, OCH_3), 1.75 (m, 1H, H-6), 1.08 (t, $J_{3',2'}$ = 7.3 Hz, 3H, 3H-3'); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 201.3 (C-1'), 172.0 (C-3), 170.2 (CH_3CO), 143.0 (C-9), 140.4 (C-8), 71.7 (C-1), 66.0 (C-9a), 38.7 (C-5), 37.2 (C-2), 30.8 (C-2'), 24.5 (C-6), 22.8 (C-7), 21.0 (CH_3CO), 8.3 (C-3'); HRMS (ESI+) calcd for $[C_{14}H_{19}NO_4Na^+]$: 288.1212, found: 288.1206.

*4.30. (E)-6-(2-Ethoxy-5-oxopyrrolidin-1-yl)hex-2-enal (**50**)*

Freshly distilled acrolein (394 µL, 5.96 mmol) and a solution of HG-II catalyst (41 mg, 0.05 mmol) in dry and degassed CH_2Cl_2 (0.8 mL) under nitrogen atmosphere were added to a solution of aminal **49** (392 mg, 1.99 mmol) in dry and degassed CH_2Cl_2 (4 mL), under nitrogen atmosphere, at room temperature. The resulting green solution was stirred at room temperature for 1 h. Then, an additional portion of catalyst (41 mg, 0.05 mmol, 2.5 mol%) in dry and degassed CH_2Cl_2 (0.8 mL) was added to the brown solution and the mixture was stirred for 1 hour more. After this time, TLC analysis of the reaction mixture (EtOAc) did not show starting aminal **49**. The reaction mixture was filtered through silica gel, washing with EtOAc. The organic solvent was evaporated under vacuum and the remaining brown oil was purified by column chromatography (hexanes/EtOAc, 1:1) to afford aldehyde **50** as a pale yellow oil (400 mg, 1.78 mmol, 89%): R_f 0.18 (EtOAc); IR (ATR) 3340, 2931, 2360, 2052, 1954, 1673, 1420, 1374, 1344, 1280, 1161, 1131, 1069, 976 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.50 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 6.85 (dt, $J_{3,2}$ = 15.6 Hz, $J_{3,4}$ = 6.6 Hz, 1H, H-3), 6.13 (dd, $J_{2,3}$ = 15.6 Hz, $J_{2,1}$ = 7.8 Hz, 1H, H-2), 4.94 (dd, $J_{2',3'}$ = 6.2 Hz, $J_{2',3'}$ = 1.3 Hz, 1H, H-2'), 3.44 (m, 3H, H-6, 2H-1''), 3.24 (ddd, $J_{6,6}$ = 14.0 Hz, $J_{6,5}$ = 7.6 Hz, $J_{6,5}$ = 6.3 Hz, 1H, H-6), 2.53 (dt, $J_{4',3'}$ = 17.6 Hz, $J_{4',4'}$ = 8.9 Hz, 1H, H-4'), 2.15 (m, 5H, 2H-4, 2H-3', H-4'), 1.77 (m, 2H, 2H-5), 1.22 (t, $J_{2'',1''}$ = 7.0 Hz, 3H, 3H-2''); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 193.8 (C-1), 175.1 (C-5'), 157.3 (C-3), 133.2 (C-2), 89.4 (C-2'), 61.4 (C-1''), 40.2 (C-6), 30.1/28.9/26.2/24.8 (C-4'/C-5/C-3'/C-4), 15.3 (C-2''); HRMS (ESI+) calcd for $[C_{12}H_{19}NO_3Na^+]$: 248.1257, found: 248.1262.

*4.31. 3-Oxo-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carbaldehyde (**51**)*

In a schlenk vessel connected to a nitrogen line, aldehyde **50** (5.85 g, 26 mmol) was solved in dry acetonitrile (160 mL) and the solution cooled down to –50 °C. At this temperature, Me_2S (3.29 mL, 44.5 mmol) and TMSOTf (13.4 mL, 73.9 mmol) were added and the resulting mixture was allowed to warm to room temperature and stirred overnight. After this time, the reaction was quenched with saturated aqueous $NaHCO_3$ (80 mL). After evaporation of the acetonitrile under vacuum, the remaining aqueous solution was extracted with CH_2Cl_2 (3x40 mL). The organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography (EtOAc) to afford aldehyde **51** as a pale white solid (4.81 g, 26 mmol, quantitative): R_f 0.34 (EtOAc/MeOH, 10:1, silica gel); R_f 0.36 (EtOAc, neutral alumina); IR (ATR) 2947, 2866, 2360, 1991, 1668, 1638, 1454, 1418, 1390, 1356, 1318, 1265, 1223, 1181, 1150, 1073, 1030, 972 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.37 (s, 1H, H-1'), 6.84 (dd, $J_{8,7}$ = 8.2, $J_{8,7}$ = 5.1 Hz, 1H, H-8), 4.59 (bt, $J_{9a,4}$ = 6.7 Hz, 1H, H-9a), 4.18 (ddd, $J_{5,5}$ = 14.0, $J_{5,6}$ = 7.9 Hz, $J_{5,6}$ = 4.4 Hz, 1H, H-5), 2.85 (ddd, $J_{5,5}$ = 14.0, $J_{5,6} \approx J_{5,6}$ = 7.6 Hz, 1H, H-5), 2.57 (m, 2H, H-1, H-7), 2.39 (m, 3H, 2H-2, H-7), 2.12 (m, 1H, H-6), 1.81 (m, 2H, H-4, H-6); ^{13}C NMR (90.0 MHz, $CDCl_3$) δ 193.5 (C-1'), 175.0 (C-2), 152.9 (C-8), 145.3 (C-9), 59.2 (C-9a), 39.2 (C-5), 30.1 (C-7), 25.8/24.5/24.3 (C-3/C-4/C-8); HRMS (ESI+) calcd for $[C_{10}H_{13}NO_2Na^+]$: 202.0844, found: 202.0838.

*4.32. (E)-8-(5-Ethoxy-2-oxo-pyrrolidin-1-yl)-4-octen-3-one (**52**)*

1-Penten-3-one (155 µl, 1.57 mmol) was added to a solution of aminal **49** (103 mg, 0.52 mmol) in dry and degassed CH_2Cl_2 (1.2 mL) under nitrogen atmosphere. Then, a solution of HG-II catalyst (17 mg, 0.025 mmol) in dry and degassed CH_2Cl_2 (0.3 mL) was added dropwise at room temperature. The resulting green solution was stirred for 1 h at room temperature. Then, an additional portion of catalyst (17 mg, 0.025 mmol, 5 mol%) in dry and degassed CH_2Cl_2 (0.3 mL) was added to the brown solution and the mixture was stirred for an additional hour. After this time, TLC analysis of the reaction mixture (EtOAc) did not show starting aminal **49**. The mixture was filtered through a silica pad, washing with EtOAc. The organic solvent was evaporated under vacuum and the remaining brown oil was purified by column chromatography (hexanes/EtOAc, 1:1) to afford ketone **52** as a pale yellow oil (100 mg, 0.39 mmol, 76%): R_f 0.30 (EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.81 (dt, $J_{4,5}$ = 15.9 Hz, $J_{4,3}$ = 6.8 Hz, 1H, H-4), 6.13 (dt, $J_{5,4}$ = 15.9 Hz, $J_{5,3}$ = 1.4 Hz, 1H, H-5), 4.94 (dd, $J_{5',4'}$ = 6.0 Hz, $J_{5',4'}$ = 1.4 Hz, 1H, H-5'), 3.44 (m, 3H, 2H-1'', H-1), 3.18 (ddd, $J_{1,1}$ = 13.9 Hz, $J_{1,2}$ = 7.8 Hz, $J_{1,2}$ = 6.2 Hz, 1H, H-1), 2.54 (q, $J_{7,8}$ = 7.3 Hz, 2H, H-7), 2.51 (m, 1H, H-3'), 2.36 - 1.90 (m, 5H, 2H-3, 2H-4', H-3'), 1.72 (m, 2H, 2H-2), 1.21 (t, $J_{2'',1''}$ = 7.0 Hz, 3H, 3H-2''), 1.08 (t, $J_{8,7}$ = 7.3 Hz, 3H, 3H-8); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 201.1 (C-6), 175.2 (C-2'), 145.6 (C-4), 130.4 (C-5), 89.4 (C-5'), 61.5 (CH_3CH_2), 40.3 (C-1), 33.5 (C-7), 29.9 (C-3), 29.1 (C-4'), 26.4 (C-2), 24.9 (C-3'), 15.4 (CH_3CH_2), 8.2 (C-8); HRMS (ESI+) calcd for $[C_{14}H_{23}NO_3H^+]$: 254.1756, found: 254.1743.

*4.33. 5-(3-Oxo-1-penten-2-yl)-1-(4-penten-1-yl)pyrrolidin-2-one (**54**)*

In a schlenk vessel connected to a nitrogen line, aminal **49** (580 mg, 2.94 mmol) was solved in dry acetonitrile (13 mL) and cooled down to –50 °C. At this temperature, 1-penten-3-one (437 µL, 4.41 mmol), Me_2S (326 µL, 4.41 mmol) and TMSOTf (1.32 mL, 7.32

mmol) were added and the resulting mixture was allowed to warm up to room temperature and stirred overnight. After this time, the reaction was quenched with saturated aqueous $NaHCO_3$ (8 mL). After evaporation of the acetonitrile under vacuum, the mixture was extracted with CH_2Cl_2 (3x6 mL) and the combined organic extracts dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography (EtOAc) to afford lactam **54** as a yellowish syrup (610 mg, 2.59 mmol, 88%): R_f 0.14 (EtOAc); IR (ATR) 3368, 3076, 2974, 2936, 1671, 1457, 1416, 1373, 1097 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.18 (bs, 1H, H-1''), 5.77 (ddd, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.7 Hz, $J_{4',5'}$ = 3.0 Hz, 1H, H-4'), 5.65 (bs, 1H, H-1''), 4.99 (m, 2H, 2H-5'), 4.69 (bd, $J_{5,4}$ = 6.9 Hz, 1H, H-5), 3.73 (dt, $J_{1',1'}$ = 13.7 Hz, $J_{1',2'}$ = 7.9 Hz, 1H, H-1'), 2.77 (m, 2H, 2H-4''), 2.59 (dt, $J_{1',1'}$ = 13.7 Hz, $J_{1',2'}$ = 7.1 Hz, 1H, H-1'), 2.30 (m, 2H, 2H-4), 2.01 (m, 2H, 2H-3'), 1.60 (m, 4H, 2H-3, 2H-2'), 1.13 (t, $J_{5'',4''}$ = 7.3Hz, 3H, 3H-5''); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 201.6 (C-3''), 175.9 (C-2'), 146.8 (C-2''), 137.7 (C-4), 123.4 (C-1''), 115.3 (C-5), 56.9 (C-5'), 40.6 (C-1), 31.5/31.2/29.3/26.6/26.2 (C-2/C-3/C-3'/C-4'/C-4''), 8.3 (C-5''); HRMS (ESI+) calcd for $[C_{14}H_{21}NO_2Na^+]$: 258.1470, found: 258.1465.

*4.34. 9-(1-Hydroxypropyl)-5,6,7,9a-tetrahydro-1H-pyrrolo[1,2-a]azepin-3(2H)-one (**55**)*

Aldehyde **51** (105 mg, 590 µmol) was dissolved in dry THF (2 mL) and cooled down to –20 °C under nitrogen atmosphere. Ethyl magnesium bromide (3M in Et_2O, 234 µL, 700 µmol) was added dropwise and the resulting mixture was stirred overnight at –20 °C. Then, the reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL) and diluted with Et_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The organic fractions were combined, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residual oil was purified by column chromatography (EtOAc) to yield a mixture of two diastereoisomers (4:1) of alcohol **55** as a pale yellow syrup (107 mg, 0.51 mmol, 88%): R_f 0.22 (CH_2Cl_2/MeOH, 20:1); IR (ATR) 3371, 2934, 2870, 1657, 1459, 1420 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.80 (dd, $J_{8,7}$ = 8.7 Hz, $J_{8,7}$ = 6.2 Hz) and 5.73 (dd, $J_{8,7}$ = 8.8 Hz, $J_{8,7}$ = 5.8 Hz) (1H, H-8), 4.26 (m, 1H, H-9a), 4.01 (m, 2H, H-1', H-5), 2.85 (ddd, $J_{5,5}$ = 13.8 Hz, $J_{5,6}$ = 9.6 Hz, $J_{5,6}$ = 7.9 Hz, 1H, H-5), 2.50 - 1.50 (m, 10H, 2H-1, 2H-2, 2H-6, 2H-7, 2H-2'), 0.94 (t, $J_{3',2'}$ = 7.4 Hz, 3H, 3H-3'); HRMS (ESI+) Calcd for $[C_{12}H_{19}NO_2Na^+]$: 232.1308, found: 232.1312.

*4.35. 9-Propionyl-5,6,7,9a-tetrahydro-1H-pyrrolo[1,2-a]azepin-3(2H)-one (**53**)*

A commercially available solution of DMPI in CH_2Cl_2 (15% wt, 885 µL, 0.42 mmol) was added via syringe to a solution of alcohol **55** (70 mg, 0.33 mmol) in dry CH_2Cl_2 (6 mL) at room temperature under nitrogen atmosphere. After stirring for 2 h at room temperature, TLC analysis (EtOAc) indicated the complete consumption of the starting material. The reaction was quenched with 3 mL of a solution prepared by addition of $Na_2S_2O_3$ (17 g) to a saturated aqueous solution of $NaHCO_3$ (90 mL) and the mixture was stirred for 15 min. The aqueous phase was extracted with CH_2Cl_2 (2x8 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Column chromatography (EtOAc) of the resulting oil provided ketone **53** as a yellow syrup (60 mg, 0.29 mmol, 86%): R_f 0.18 (EtOAc); IR (ATR) 2937, 2873, 1660, 1458, 1418, 1458, 1418, 1227 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (dd, $J_{8,7}$ = 9.0 Hz, $J_{8,7}$ = 5.4 Hz, 1H, H-8), 4.68 (m, 1H, H-9a), 4.09 (ddd, $J_{5,5}$ = 14.0 Hz, $J_{5,6}$ = 8.7 Hz, $J_{5,6}$ = 3.3 Hz, 1H, H-5), 2.84 (dt, $J_{5,5}$ = 14.0 Hz, $J_{5,6}$ = 8.2 Hz, 1H, H-5), 2.66 (m, 2H, 2H-2'), 2.43 (m, 4H, H-1, H-7, 2H-2), 2.14 (m, 2H, H-6, H-7), 1.70 (m, 2H, H-1, H-6), 1.08 (t, $J_{3',2'}$ = 7.3 Hz, 3H, 3H-3'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5 (C-1'), 175.1 (C-3), 143.6 (C-9), 140.4 (C-8), 60.9 (C-9a), 38.7 (C-5), 30.7/30.4 (C-2/C-2'), 26.9 (C-1), 24.1 (C-6), 22.7 (C-7), 8.6 (C-3'); HRMS (ESI+) calcd for $[C_{12}H_{17}NO_2Na^+]$: 230.1151, found: 230.1154.

*4.36. (3S)-3-Hydroxy-1-(4-penten-1-yl)-2,5-pyrrolidinedione (**56**)*

Acetyl chloride (8 ml, 0.12 mol) was added dropwise to a solution of imide **43** (1.31 g, 5.77 mmol) in EtOH at 0 °C. The mixture was stirred for 3 h at room temperature and then concentrated under reduced pressure. Benzene was added and then the solution concentrated *in vacuo* (this procedure was repeated 3 times) affording **56**[30] as a yellow syrup (1.06 g, 5.77 mmol, quantitative): ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, $J_{4',5'}$ = 16.9 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.5 Hz, 1H, H-4'), 5.00 (dd, $J_{4',5'}$ = 17.1 Hz, $J_{5',5'}$ = 1.3 Hz, 1H, H-5'), 4.96 (dd, $J_{5',4'}$ = 10.2 Hz, $J_{5',5'}$ = 1.2 Hz, 1H, H-5'), 4.63 (dd, $J_{3,4}$ = 8.5 Hz, $J_{3,4}$ = 4.8 Hz, 1H, H-3), 4.27 (s, 1H, OH), 3.55 - 3.38 (m, 2H, 2H-1'), 3.04 (dd, $J_{4,4}$ = 18.2 Hz, $J_{4,3}$ = 8.4 Hz, 1H, H-4), 2.65 (dd, $J_{4,4}$ = 18.2 Hz, $J_{4,3}$ = 4.8 Hz, 1H, H-4), 2.03 (dd, $J_{3',2'}$ = 14.6 Hz, $J_{4',3'}$ = 6.8 Hz, 2H, 2H-3'), 1.65 (dt, $J_{3',2'}$ = 14.8 Hz, $J_{2',1'}$ = 7.5 Hz, 2H, 2H-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7/174.3 (C-2/C-5), 136.9 (C-4'), 115.4 (C-5'), 66.7 (C-3), 38.4 (C-1'), 37.1 (C-4), 30.8 (C-3'), 26.5 (C-2').

*4.37. (3S)-3-Benzyloxy-1-(4-penten-1-yl)-2,5-pyrrolidinedione (**57a**)*

Benzyl bromide (345 µl, 2.90 mmol) and silver oxide (672 mg, 2.90 mmol) were added to a solution of **56** (177 mg, 0.97 mmol) in diethyl ether (6 mL). After stirring at dark for two days at room temperature, the mixture was filtered through Celite® and concentrated *in vacuo*. Column chromatography (hexanes/EtOAc, 6:1 to 1:1) of the crude material afforded **57a**[30] as a colourless oil (257 mg, 0.94 mmol, 97%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.31 (m, 5H, 5H-Ar), 5.79 (ddt, $J_{4',5'}$ = 16,9 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.5 Hz, 1H, H-4'), 5.04 (d, $J_{4',5'}$ = 17.2 Hz, 1H, H-5'), 4.99 (d, J = 11.5 Hz, 2H, H-5', ArCH_2O), 4.79 (d, J = 11.5 Hz, 1H, ArCH_2O), 4.34 (dd, $J_{3,4}$ = 8.2 Hz, $J_{3,4}$ = 4.1 Hz, 1H, H-3), 3.54 (t, $J_{1',2'}$ = 7.5 Hz, 2H, 2H-1'), 2.92 (dd, $J_{4,4}$ = 18.2 Hz, $J_{3,4}$ = 8.2 Hz, 1H, H-4), 2.64 (dd, $J_{4,4}$ = 18.2 Hz, $J_{3,4}$ = 4.1 Hz, 1H, H-4), 2.09 (m, 2H, 2H-3'), 1.75 - 1.67 (m, 2H, 2H-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8/174.1 (C-2/C-5), 137.0 (C-4'), 136.6 (C-Ar), 128.5 (C-Ar), 128.2 (C-Ar), 115.4 (C-5'), 73.1 (ArCH$_2$O), 71.8 (C-3), 38.8 (C-1'), 36.1 (C-4), 30.8 (C-3'), 26.5 (C-2').

*4.38. (S)-3-[(4-Methoxybenzyl)oxy]-1-(4-penten-1-yl)-2,5-pyrrolidinedione (**57b**)*

p-Methoxybenzyl chloride (770 µl, 5.62 mmol) and silver oxide (1.30 g, 5.62 mmol) were added to a solution of **56** (343 mg, 1.87 mmol) in diethyl ether (12 mL). After stirring at dark for two days at room temperature, the mixture was filtered through Celite® and concentrated *in vacuo*. Column chromatography (hexanes/EtOAc, 6:1 to 1:1) of the crude material afforded **57b** as a colourless oil (522 mg, 1.72 mmol, 92%): $[\alpha]_D$ +36.3 (*c* 1.26, $CHCl_3$); IR (ATR): 3015, 2933, 2839, 1704, 1586, 1514, 1440, 1402, 1343, 1248, 1174, 1113, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, $J_{ortho,meta}$ = 8.6 Hz, 2H, 2H-Ar), 6.91 (d, $J_{ortho,meta}$ = 8.6 Hz, 2H, 2H-Ar), 5.80 (ddt, $J_{4',5'}$ = 16.9 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.5 Hz, 1H, H-4'), 5.06 (dq, $J_{4',5'}$ = 17.2 Hz, $J_{5',3'}$ = $J_{5',5'}$ = 1.5 Hz, 1H, H-5'), 5.00 (ddd, $J_{5',4'}$ = 10.2 Hz, $J_{5',3'}$ = 3.4 Hz, $J_{5',5'}$ = 1.5 Hz, 1H, H-5'), 4.93 (d, J = 11.3 Hz, 1H, ArCH_2O), 4.74 (d, J = 11.3 Hz, 1H, ArCH_2O), 4.34 (dd, $J_{3,4}$ = 8.2 Hz, $J_{3,4}$ = 4.1 Hz, 1H, H-3), 3.83 (s, 3H, CH_3O), 3.51 (t, $J_{1',2'}$ = 7.5 Hz, 2H, 2H-1'), 2.90 (dd, $J_{4,4}$ = 18.2 Hz, $J_{3,4}$ = 8.2 Hz, 1H, H-4), 2.63 (dd, $J_{4,4}$ = 18.2 Hz, $J_{3,4}$ = 4.1 Hz, 1H, H-4), 2.07 (m, 2H, 2H-3'), 1.68 (qn, $J_{3',2'}$ = $J_{2',1'}$ = 7.5 Hz, 2H, 2H-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0/174.2 (C-2/C-5), 159.6 (CH_3OC), 137.1 (C-4'), 129.9 (C-Ar), 128.7 (C-Ar), 115.4

(C-5'), 113.9 (C-Ar), 72.6 (Ar*C*H_2O), 71.6 (C-3), 55.2 (CH_3O), 38.2 (C-1'), 36.2 (C-4), 30.8 (C-3'), 26.5 (C-2'); HRMS (EI): calcd for [$C_{17}H_{21}NO_4^+$]: 303.1471; found: 303.1465.

4.39. *(S)-2,5-Dioxo-1-(4-penten-1-yl)pyrrolidin-3-yl pivalate* ***(57c)***

Pivaloyl chloride (240 µl, 1.92 mmol) was added to a solution of **56** (176 mg, 0.96 mmol) in dry CH_2Cl_2 (4 mL) containing triethylamine (1.3 ml, 9.60 mmol) at 0 °C. The reaction was allowed to reach room temperature and stirred overnight. Then, it was poured into 2M HCl (4 mL) and extracted with CH_2Cl_2 (2x5 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude material was purified by column chromatography (hexanes/EtOAc, from 6:1 to 1:1) affording **57c** as a brown oil (205 mg, 0.77 mmol, 80%): $[\alpha]_D$ –7.9 (*c* 1.70, $CHCl_3$); IR (ATR): 2975, 1714, 1403, 1281, 1144 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, $J_{4',5'}$ = 16.9 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.8 Hz, 1H, H-4'), 5.36 (dd, $J_{3,4}$ = 8.7 Hz, $J_{3,4}$ = 4.8 Hz, 1H, H-3), 5.04 (d, $J_{4',5'}$ = 17.0 Hz, 1H, H-5'), 4.98 (d, $J_{5',4'}$ = 10.2 Hz, 1H, H-5'), 3.55 (t, $J_{1',2'}$ = 7.5 Hz, 2H, 2H-1'), 3.11 (dd, $J_{4,4}$ = 18.3 Hz, $J_{3,4}$ = 8.7 Hz, 1H, H-4), 2.60 (dd, $J_{4,4}$ = 18.2 Hz, $J_{3,4}$ = 4.8 Hz, 1H, H-4), 2.07 (q, $J_{3',4'}$ = $J_{3',2'}$ = 7.2 Hz, 2H, 2H-3'), 1.71 (qn, $J_{3',2'}$ = $J_{2',1'}$ = 7.5 Hz, 2H, 2H-2'), 1.23 (s, 9H, Me_3C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4 (^{t}Bu*C*O), 173.5/173.2 (C-2/C-5), 137.0 (C-4'), 115.4 (C-5'), 67.3 (C-3), 38.7 (Me$_3$*C*), 38.6 (C-1'), 35.5 (C-4), 30.8 (C-3'),26.7 (3C, *Me*$_3$C), 26.4 (C-2'); HRMS (ESI+): calcd for [$C_{14}H_{21}NO_4Na^+$]: 290.1363, found: 290.1361.

4.40. *(S)-2,5-Dioxo-1-(4-penten-1-yl)pyrrolidin-3-yl benzoate* ***(57d)***

Benzoyl chloride (155 µl, 1.33 mmol) was added to a solution of **56** (222 mg, 1.21 mmol) in dry CH_2Cl_2 (5 mL) containing triethylamine (185 µL, 1.33 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature and stirred overnight. Then, it was poured into 2M HCl (5 mL) and extracted with CH_2Cl_2 (2x5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, from 7:1 to 1:1) affording **57d** as a brown oil (300 mg, 1.05 mmol, 86%): $[\alpha]_D$ +11.5 (*c* 1.00, $CHCl_3$); IR (ATR) 2942, 1711, 1453, 1405, 1350, 1271, 1180, 1117, 1070, 1029, 916 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 - 7.94 (m, 2H, 2H-Ar), 7.61 - 7.51 (m, 1H, H-Ar), 7.48 - 7.35 (m, 2H, 2H-Ar), 5.78 (ddt, $J_{4',5'}$ = 17.2 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.6 Hz, 1H, H-4'), 5.60 (dd, $J_{3,4}$ = 8.7 Hz, $J_{3,4}$ = 4.8 Hz, 1H, H-3), 5.00 (m, 2H, 2H-5'), 3.55 (m, 2H, 2H-1'), 3.23 (dd, $J_{4,4}$ = 18.3 Hz, $J_{3,4}$ = 8.7 Hz, 1H, H-4), 2.77 (dd, $J_{4,4}$ = 18.4 Hz, $J_{3,4}$ = 4.9 Hz, 1H, H-4), 2.08 (m, 2H, 2H-3'), 1.71 (qn, $J_{3',2'}$ = $J_{2',1'}$ = 7.5 Hz, 2H, 2H-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4/173.2 (C-2/C-5), 165.4 (Ar*C*O), 137.0 (C-4'), 133.8 (C-Ar), 129.9 (C-Ar), 128.5 (C-Ar), 128.4 (C-Ar), 115.4 (C-5'), 68.0 (C-3), 38.7 (C-1'), 35.7 (C-4), 29.6 (C-3'), 26.4 (C-2'); HRMS (ESI+) calcd for [$C_{16}H_{17}NO_4Na^+$]: 310.1050, found: 310.1055.

4.41. *(S)-3-(tert-Butyldimethylsilyl)oxy-1-(4-penten-1-yl)-2,5-pyrrolidinedione* ***(57e)***

TBS-Imidazole (430 µL, 2.20 mmol) was added dropwise to a solution of **56** (366 mg, 2.00 mmol) in CH_2Cl_2 (3 mL) and the mixture was stirred overnight at room temperature. Then, 0.1M HCl (3 mL) was added and the organic layer was washed with water (3 mL) and brine (3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (hexanes/EtOAc, from 8:1 to 1:1) affording **57e** as a brown oil (547 mg, 1.84 mmol, 92%): $[\alpha]_D$ –30.1 (*c* 1.36, $CHCl_3$); IR (ATR) 2930, 2857, 1709, 1439, 1401, 1346, 1252, 1129, 941 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (ddt, $J_{4',5'}$ = 16.9 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.8 Hz, 1H, H-4'), 4.96 (dd, $J_{4',5'}$ = 17.2 Hz, $J_{5',5'}$ = 1.7 Hz, 1H, H-5'), 4.91 (dd, $J_{5',4'}$ = 10.2 Hz, $J_{5',5'}$ = 1.7 Hz, 1H, H-5'), 4.51 (dd, $J_{3,4}$ = 8.1 Hz, $J_{3,4}$ = 4.4 Hz, 1H, H-3), 3.43 (t, $J_{1',2'}$ = 7.5 Hz, 2H, 2H-1'), 2.92 (dd, $J_{4,4}$ = 17.9 Hz, $J_{3,4}$ = 8.1 Hz, 1H, H-4), 2.50 (dd, $J_{4,4}$ = 17.9 Hz, $J_{3,4}$ = 4.5 Hz, 1H, H-4), 1.99 (q, $J_{3',4'}$ = $J_{3',2'}$ = 6.9 Hz, 2H, 2H-3'), 1.61 (qn, $J_{3',2'}$ = $J_{2',1'}$ = 7.4 Hz, 2H, 2H-2'), 0.85 (s, 9H, *Me*$_3$C), 0.12 (s, 3H, C*H*$_3$Si), 0.11 (s, 3H, C*H*$_3$Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5/174.0 (C-2/C-5), 137.0 (C-4'), 115.2 (C-5'), 67.7 (C-3), 38.7 (C-1'), 38.6 (C-4), 30.1 (C-3'), 26.5 (C-2'), 25.5 (3C, *Me*$_3$C), 18.1 Me$_3$*C*), –4.8 (*C*H$_3$Si), –5.4 (*C*H$_3$Si); HRMS (ESI+) calcd for [$C_{15}H_{27}NO_3SiNa^+$]: 320.1652, found: 320.1650.

4.42. *(S)-3-(tert-Butyldiphenylsilyl)oxy-1-(4-penten-1-yl)-2,5-pyrrolidinedione,* ***(57f)***

TBDPSCl (1.74 ml, 6.68 mmol) was added dropwise to a solution of **56** (1.20 g, 6.55 mmol) in CH_2Cl_2 (9 mL) containing imidazole (464 mg, 6.81 mmol) and the mixture was stirred overnight at room temperature. Then, 0.1M HCl (10 mL) was added and the organic layer was washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (hexanes/EtOAc, from 8:1 to 1:1) affording **57f** as a yellow oil (2.49 g, 5.90 mmol, 90%): $[\alpha]_D$ –1.4 (*c* 1.39, $CHCl_3$); IR (ATR) 2931, 2858, 1711, 1428, 1402, 1362, 1113 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 - 7.80 (m, 2H-Ar), 7.73 - 7.66 (m, 2H-Ar), 7.52 - 7.37 (m, 6H-Ar), 5.79 (ddt, $J_{4',5'}$ = 16.9 Hz, $J_{4',5'}$ = 10.3 Hz, $J_{4',3'}$ = 6.6 Hz, 1H, H-4'), 5.04 (dd, $J_{4',5'}$ = 17.2 Hz, $J_{5',5'}$ = 1.7 Hz, 1H, H-5'), 4.99 (dd, $J_{5',4'}$ = 10.3 Hz, $J_{5',5'}$ = 1.7 Hz, 1H, H-5'), 4.54 (dd, $J_{3,4}$ = 7.9 Hz, $J_{3,4}$ = 5.0 Hz, 1H, H-3), 3.51 (m, 2H, 2H-1'), 2.66 (dd, $J_{4,4}$ = 17.9 Hz, $J_{3,4}$ = 7.9 Hz, 1H, H-4), 2.57 (dd, $J_{4,4}$ = 17.9 Hz, $J_{3,4}$ = 5.0 Hz, 1H, H-4), 2.07 (q, $J_{3',4'}$ = $J_{3',2'}$ = 6.9 Hz, 2H, 2H-3'), 1.69 (qn, $J_{3',2'}$ = $J_{2',1'}$ = 7.4 Hz, 2H, 2H-2'), 1.13 (s, 9H, Me_3C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3 (C-2), 173.9 (C-5), 137.9 (C-4'), 135.9 (C-Ar), 135.6 (2C-Ar), 132.8 (C-Ar), 131.9 (C-Ar), 130.2 (C-Ar), 130.1 (C-Ar), 127.9 (C-Ar), 127.8 (C-Ar), 115.3 (C-5'), 68.2 (C-3), 38.7/38.3 (C-4/C-1'), 30.9 (C-3'), 26.7 (*Me*$_3$C), 26.5 (C-2'), 19.1 (Me$_3$*C*); HRMS (ESI+) calcd for [$C_{25}H_{31}NO_3SiNa^+$]: 444.1965, found: 444.1960.

4.43. *General procedure for the reduction of imides* ***57*** *to acylaminals* ***58***

To a 0.4M solution of the imide in MeOH at –20 °C was added $NaBH_4$ (2.5 mol per mol of imide) and the mixture was stirred at this temperature for 2 h. Then, a saturated aqueous solution of $NaHCO_3$ (same volume as MeOH) was added carefully and the mixture was stirred at room temperature for 5 min. The volatiles were removed under vacuum and the aqueous layer was extracted twice with CH_2Cl_2 (same volume as MeOH), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

4.44. *(S)-4-Benzyloxy-5-hydroxy-1-(4-pentenyl)-2-pyrrolidinone* ***(58a)***

Following the general procedure, from **57a** (169 mg, 619 µmol), after column chromatography (hexanes/EtOAc, from 3:1 to 1:3) of the crude product, two diastereoisomers of **58a** were isolated as a brown oil (148 mg, 539 µmol, 85%). HRMS (EI) calcd for [$C_{16}H_{21}NO_3^+$]: 275.1521, found. 275.1516. Analytical samples of each isomer were isolated by repeated chromatography. **58a*lp*** (less polar): $[\alpha]_D$ +25.2 (*c* 1.18, $CHCl_3$); IR (ATR) 3347, 2929, 1701, 1457, 1352, 1078, 915 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.30 (m, 5H-Ar), 5.79 (ddt, $J_{4',5'}$ = 17.0 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.3 Hz, 1H, H-4'), 5.13 (d, $J_{5,4}$ = 6.1 Hz, 1H, H-5), 5.03 (dd, $J_{4',5'}$ = 17.0 Hz, $J_{5',5'}$ = 0.9 Hz, 1H, H-5'), 4.97 (dd, $J_{5',4'}$

= 10.2 Hz, $J_{5',5'}$ = 0.9 Hz, 1H, H-5'), 4.61 (s, 2H, ArCH_2O), 4.11 (m, 1H, H-4), 3.77 (bs, 1H, OH), 3.44 (dt, $J_{1',1'}$ = 14.5 Hz, $J_{1',2'}$ = 7.3 Hz, 1H, H-1'), 3.26 (dt, $J_{1',1'}$ = 14.5 Hz, $J_{1',2'}$ = 7.1 Hz, 1H, H-1'), 2.52 (m, 2H, 2H-3), 2.06 (q, $J_{3',2'} = J_{3',4'}$ = 7.0 Hz, 2H, 2H-3'), 1.64 (m, 2H, 2H-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (C-2), 137.6 (C-4'), 136.6 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 127.9 (C-Ar), 115.0 (C-5'), 82.2 (C-5), 72.0 (Ar*C*H_2O), 71.7 (C-4), 39.9 (C-1'), 35.7 (C-3), 31.1 (C-3'), 26.9 (C-2'). **58a*mp*** (more polar): $[\alpha]_D$ +38.2 (*c* 1.51, $CHCl_3$); IR (ATR): 3347, 2929, 1701, 1457, 1352, 1078, 915 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.29 (m, 5H-Ar), 5.80 (ddt, $J_{4',5'}$ = 17.3 Hz, $J_{4',5'}$ = 10.4 Hz, $J_{4',3'}$ = 6.8 Hz, 1H, H-4'), 5.13 (s, 1H, H-5), 5.03 (d, $J_{4',5'}$ = 17.3 Hz, 1H, H-5'), 4.98 (d, $J_{5',4'}$ = 10.4 Hz, 1H, H-5'), 4.60 (s, 2H, ArCH_2O), 4.08 (bs, 1H, OH), 3.97 (dd, $J_{4,3}$ = 6.4 Hz, $J_{4,3}$ = 2.2 Hz, 1H, H-4), 3.50 (dt, $J_{1',1'}$ = 13.6 Hz, $J_{1',2'}$ = 7.8 Hz, 1H, H-1'), 3.16 (dt, $J_{1',1'}$ = 13.8 Hz, $J_{1',2'}$ = 7.2 Hz, 1H, H-1'), 2.78 (dd, $J_{3,3}$ = 17.6 Hz, $J_{3,4}$ = 6.8 Hz, 1H, H-3), 2.39 (dd, $J_{3,3}$ = 17.5 Hz, $J_{3,4}$ = 2.5 Hz, 1H, H-3), 2.07 (q, $J_{3',2'} = J_{3',4'}$ = 7.3 Hz, 2H, 2H-3'), 1.61 (m, 2H, 2H-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 (C-2), 137.6 (C-4'), 137.4 (C-Ar), 128.5 (C-Ar), 127.9 (C-Ar), 127.6 (C-Ar), 115.1 (C-5'), 87.5 (C-5), 78.8 (C-4), 71.3 (Ar*C*H_2O), 39.4 (C-1'), 36.3 (C-3), 30.9 (C-3'), 26.7 (C-2').

*4.45. (S)-5-Hydroxy-4-(4-methoxybenzyl)oxy-1-(4-pentenyl)-2-pyrrolidinone (**58b**)*

Following the general procedure, from **57b** (71 mg, 234 μmol), after column chromatography (hexanes/EtOAc, from 3:1 to 1:3) of the crude product, two diastereoisomers of **58b** were isolated as a brown oil (43 mg, 143 μmol, 61%): IR (ATR) 2927, 1689, 1613, 1514, 1461, 1249, 1174, 1080 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 - 7.24 (m, 2H-Ar), 6.95 - 6.86 (m, 2H-Ar), 5.81 (ddt, $J_{4',5'}$ = 16.8 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.6 Hz, 1H, H-4'), 5.12 (d, $J_{5,4}$ = 5.7 Hz, 1H, H-5), 5.03 (d, $J_{4',5'}$ = 17.2 Hz, 1H, H-5') 4.98 (d, $J_{5',4'}$ = 10.2 Hz, 1H, H-5'), 4.55 (m, 2H, ArCH_2O), 4.12 (m, 1H, H-4), 3.83 (s, 3H, CH_3O), 3.57 (bs, 1H, OH), 3.43 (m, 1H, H-1'), 3.26 (m, 1H, H-1'), 2.51 (m, 2H, 2H-3), 2.07 (q, $J_{3',2'} = J_{3',4'}$ = 6.9 Hz, 2H, 2H-3'), 1.67 (m, 2H, 2H-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6 and 171.3 (C-2), 159.7 and 159.3 (C-Ar), 137.6 and 137.6 (C-4'), 129.7 and 129.4 (C-Ar), 129.3 and 128.5 (C-Ar), 115.1 and 115.0 (C-5'), 114.0 and 113.9 (C-Ar), 87.6 and 82.2 (C-5), 78.5 and 71.4 (C-4), 71.8 and 71.0 (Ar*C*H2O), 55.2 (*C*H_3O), 39.9 and 39.4 (C-1'), 36.3 and 35.8 (C-3), 31.1 and 30.9 (C-3'), 26.9 and 26.7 (C-2'); HRMS (EI) calcd for [$C_{17}H_{23}NO_4^+$]: 305.1627, found: 305.1623.

*4.46. (S)-2-Hydroxy-5-oxo-1-(4-penten-1-yl)pyrrolidin-3-yl pivalate (**58c**)*

Following the general procedure, from **57c** (215 mg, 805 μmol), crystallization of the crude product in diethyl ether afforded **58c** as a white solid (156 mg, 580 μmol, 72%): $[\alpha]_D$ +20.7 (*c* 1.19, $CHCl_3$); IR (ATR) 2924, 1715, 1452, 1270, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (ddt, $J_{4',5'}$ = 16,9 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.6 Hz, 1H, H-4'), 5.32 (dd, $J_{3,2}$ = 5.4 Hz, $J_{2,OH}$ = 8.3 Hz, 1H, H-2), 5.16 (ddd, $J_{3,4}$ = 8.1 Hz, $J_{3,4}$ = 6.6 Hz, $J_{3,2}$ = 5.4 Hz, 1H, H-3), 5.04 (dq, $J_{4',5'}$ = 17.1 Hz, $J_{5',5'} = J_{3',5'}$ = 1.7 Hz, 1H, H-5'), 4.98 (dd, $J_{5',4'}$ = 10.2 Hz, $J_{5',5'}$ = 1.9 Hz, 1H, H-5'), 3.48 (ddd, $J_{1',1'}$ = 14.0 Hz, $J_{1',2'}$ = 8.8 Hz, $J_{1',2'}$ = 6.7 Hz, 1H, H-1'), 3.23 (ddd, $J_{1',1'}$ = 14.0 Hz, $J_{1',2'}$ = 8.7 Hz, $J_{1',2'}$ = 6.5 Hz, 1H, H-1'), 3.19 (d, $J_{OH,2}$ = 8.3 Hz, 1H, OH), 2.69 (dd, $J_{4,4}$ = 17.2 Hz, $J_{3,4}$ = 8.1 Hz, 1H, H-4), 2.58 (dd, $J_{4,4}$ = 17.2 Hz, $J_{3,4}$ = 6.6 Hz, 1H, H-4), 2.07 (q, $J_{3',4'} = J_{3',2'}$ = 7.5 Hz, 2H, 2H-3'), 1.69 (m, 2H, 2H-2'), 1.24 (s, 9H, Me_3C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9 (^{t}Bu*C*O), 170.8 (C-5), 137.4 (C-4'), 115.1 (C-5'), 81.8 (C-2), 67.4 (C-3), 39.9 (C-1'), 38.7 (Me_3C), 34.7 (C-4), 31.0 (C-3'), 27.0 (*Me*$_3$C), 26.8 (C-2'); HRMS (EI) calcd for [$C_{14}H_{23}NO_4^+$]: 269.1627, found: 269.1628.

*4.47. (S)-2-Hydroxy-5-oxo-1-(4-penten-1-yl)pyrrolidin-3-yl benzoate (**58d**).*

Following the general procedure, from **57d** (300 mg, 1.05 mmol), after column chromatography (hexanes/EtOAc, from 3:1 to 1:3) of the crude product, **58d** was isolated as a brown oil (236 mg, 815 μmol, 78%): $[\alpha]_D$ +38.5 (*c* 0.91, $CHCl_3$); IR (ATR) 3209, 2932, 1724, 1649, 1461, 1282, 1180, 1065 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, $J_{ortho,meta}$ = 7.5 Hz, 2H, 2H-Ar), 7.62 (t, $J_{meta,para}$ = 7.7 Hz, 1H, H-Ar), 7.48 (t, $J_{ortho,meta} = J_{meta,para}$ = 7.5 Hz, 2H, 2H-Ar), 5.82 (ddt, $J_{4',5'}$ = 16.9 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.6 Hz, 1H, H-4'), 5.45 (m, 2H, H-2, H-3), 5.06 (d, $J_{4',5'}$ = 17.1 Hz, 1H, H-5'), 5.00 (d, $J_{5',4'}$ = 10.2 Hz, 1H, H-5'), 3.52 (m, 1H, H-1'), 3.26 (m, 1H, H-1'), 2.78 (m, 2H, 2H-4), 2.09 (m, 2H, 2H-3'), 1.71 (m, 2H, 2H-2'); ^{13}C NMR (100 MHz, $CDCl_3$): 170.7 (C-5), 165.9 (Ar*C*O), 137.4 (C-4'), 133.6 (C-Ar), 129.7 (C-Ar), 128.9 (C-Ar), 128.5 (C-Ar), 115.2 (C-5'), 82.0 (C-2), 68.3 (C-3), 40.0 (C-1'), 34.7 (C-4), 31.0 (C-3'), 26.9 (C-2'); HRMS (ESI+) calcd for [$C_{16}H_{19}NO_4Na^+$]: 312.1212, found: 312.1206.

*4.48. (S)-4-(tert-Butyldimethylsilyl)oxy-5-hydroxy-1-(4-penten-1-yl)-2-pyrrolidinone (**58e**)*

Following the general procedure, from **57e** (200 mg, 672 μmol), after column chromatography (hexanes/EtOAc, from 3:1 to 1:3) of the crude product, **58e** was isolated as a yellow oil (123 mg, 410 μmol, 61%): $[\alpha]_D$ +51.4 (*c* 1.23, $CHCl_3$); IR (ATR) 3345, 2929, 2857, 1684, 1465, 1256, 1154, 1094 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, $J_{4',5'}$ = 16.8 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.6 Hz, 1H, H-4'), 5.04 - 4.92 (m, 3H, H-5, 2H-5'), 4.33 (m, 1H, H-4), 3.61 (d, $J_{5,OH}$ = 8.6 Hz, 1H, OH), 3.40 (ddd, $J_{1',1'}$ = 13.7 Hz, $J_{1',2'}$ = 8.7 Hz, $J_{1',2'}$ = 6.7 Hz, 1H, H-1'), 3.25 (ddd, $J_{1',1'}$ = 13.5 Hz, $J_{1',2'}$ = 8.8 Hz, $J_{1',2'}$ = 6.0 Hz, 1H, H-1'), 2.55 (dd, $J_{3,3}$ = 17.0 Hz, $J_{3,4}$ = 6.9 Hz, 1H, H-3), 2.36 (dd, $J_{3,3}$ = 17.0 Hz, $J_{3,4}$ = 4.3 Hz, 1H, H-3), 2.05 (q, $J_{3',4'} = J_{3',2'}$ = 6.9 Hz, 2H, 2H-3'), 1.65 (m, 2H, 2H-2'), 0.90 (s, 9H, Me_3C), 0.12 (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 (C-2), 137.7 (C-4'), 115.0 (C-5'), 82.7 (C-5), 66.3 (C-4), 39.9 (C-1'), 39.0 (C-3), 31.1 (C-3'), 26.9 (C-2'), 25.6 (*Me*$_3$C), 18.0 (Me_3C), –4.7 (CH_3Si), –5.1 (CH_3Si); HRMS (ESI+) calcd for [$C_{15}H_{29}NO_3SiNa^+$]: 322.1809, found: 322.1807.

*4.49. (S)-4-(tert-Butyldiphenylsilyl)oxy-5-hydroxy-1-(4-penten-1-yl)-2-pyrrolidin-2-one (**58f**)*

Following the general procedure, from **57f** (2.93 g, 6.96 mmol), after column chromatography (hexanes/EtOAc, from 5:1 to 1:3) of the crude product, two diastereoisomers of **58f** (1.97 g, 4.66 mmol, 67%) were isolated as a yellow oil and one regioisomer **58f*regio*** (326 mg, 0.77 mmol, 11%) as a brown oil. Analytical samples of each diastereoisomer of **58f** were isolated by repeated chromatography. **58f** (mixture): HRMS (ESI+) calcd for [$C_{25}H_{33}NO_3SiNa^+$]: 446.2122, found 446.2113. **58f*lp*** (less polar): $[\alpha]_D$ +15.2 (*c* 1.08, $CHCl_3$); IR (ATR) 3342, 2933, 2860, 1683, 1430, 1366, 1264, 1113 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 - 7.64 (m, 4H, 4H-Ar), 7.53 - 7.39 (m, 6H, 6H-Ar), 5.80 (ddt, $J_{4',5'}$ = 17.0 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.6 Hz, 1H, H-4'), 5.02 (dq, $J_{4',5'}$ = 17.0 Hz, $J_{5',5'} = J_{5',3'}$ = 1.6 Hz, 1H, H-5'), 4.99 - 4.94 (m, 2H, H-5', H-2), 4.36 (dt, $J_{4,3}$ = 7.3 Hz, $J_{4,5} = J_{4,3}$ = 5.4 Hz, 1H, H-4), 3.78 (d, $J_{2,OH}$ = 6.9 Hz, 1H, OH), 3.40 (ddd, $J_{1',1'}$ = 13.7 Hz, $J_{1',2'}$ = 8.9, $J_{1',2'}$ = 6.5 Hz, 1H, H-1'), 3.30 (ddd, $J_{1',1'}$ = 13.9 Hz, $J_{1',2'}$ = 8.8 Hz, $J_{1',2'}$ = 6.0 Hz, 1H, H-1'), 2.39 (dd, $J_{3,3}$ = 17.0 Hz, $J_{3,4}$ = 5.5 Hz, 1H, H-3), 2.28 (dd, $J_{3,3}$ = 17.0 Hz, $J_{3,4}$ = 7.3 Hz, 1H, H-3), 2.06 (m, 2H, 2H-3'), 1.67 (m, 2H, 2H-2'), 1.12 (s, 9H, Me_3C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5 (C-2), 137.6 (C-4'), 135.5 (C-Ar), 135.5 (C-Ar), 132.2 (C-Ar), 132.0 (C-Ar), 130.3 (C-Ar), 130.3 (C-Ar), 128.0 (C-Ar), 128.0 (C-Ar), 115.0 (C-5'), 82.9 (C-5), 67.1 (C-4), 40.2 (C-1'), 38.2 (C-3), 31.1 (C-3'), 27.0 (C-2'), 26.8 (*Me*$_3$C),

19.1 (Me_3C). **58f*mp*** (more polar): $[\alpha]_D$ +44.3 (*c* 1.01, $CHCl_3$); IR (ATR): 3370, 2933, 2859, 1675, 1429, 1365, 1264, 1108, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 - 7.59 (m, 4H, 4H-Ar), 7.53 - 7.36 (m, 6H, 6H-Ar), 5.81 (ddt, $J_{4',5'}$ = 17.0 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.6 Hz, 1H, H-4'), 5.03 (d, $J_{4',5'}$ = 17.0 Hz, 1H, H-5'), 4.99 (d, $J_{4',5'}$ = 10.3 Hz, 1H, H-5'), 4.93 (s, 1H; H-5), 4.15 (dd, $J_{4,3}$ = 6.0 Hz, $J_{4,3}$ = 2.3 Hz, 1H, H-4), 3.51 (dt, $J_{1',1'}$ = 13.7 Hz, $J_{1',2'}$ = 7.7 Hz, 1H, H-1'), 3.08 (dt, $J_{1',1'}$ = 13.7 Hz, $J_{1',2'}$ = 6.4 Hz, 1H, H-1'), 2.59 (dd, $J_{3,3}$ = 17.0 Hz, $J_{3,4}$ = 6.3 Hz, 1H, H-3), 2.26 (dd, $J_{3,3}$ = 17.0 Hz, $J_{3,4}$ = 2.3 Hz, 1H, H-3), 2.10 (m, 2H, 2H-3'), 1.64 (m, 2H, 2H-2'), 1.08 (s, 9H, Me_3C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2 (C-2), 137.6 (C-4'), 135.6 (C-Ar), 135.5 (C-Ar), 133.1 (C-Ar), 132.9 (C-Ar), 130.0 (C-Ar), 127.8 (C-Ar), 115.1 (C-5'), 89.6 (C-5), 73.3 (C-4), 39.2/38.9 (C-3/C-1'), 30.8 (C-3'), 26.7 (C-2'), 26.7 (Me_3C), 19.0 (Me_3C). **58f*regio***: ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 - 7.81 (m, 2H, 2H-Ar), 7.76 - 7.68 (m, 2H, 2H-Ar), 7.49-7.36 (m, 6H, 6H-Ar), 5.80 (ddt, $J_{4',5'}$ = 17.0 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.6 Hz, 1H, H-4'), 5.08 - 4.89 (m, 3H, 2H-5', H-5), 4.15 (dd, $J_{3,4}$ = 7.3 Hz, $J_{3,4}$ = 4.9 Hz, 1H, H-3), 3.49 (ddd, $J_{1',1'}$ = 13.7 Hz, $J_{1',2'}$ = 8.9 Hz, $J_{1',2'}$ = 6.8 Hz, 1H, H-1'), 3.26 (ddd, $J_{1',1'}$ = 13.7 Hz, $J_{1',2'}$ = 8.7 Hz, $J_{1',2'}$ = 5.8 Hz, 1H, H-1'), 3.01 (bs, OH), 2.32 (ddd, $J_{4,4}$ = 13.9 Hz, $J_{3,4}$ = 7.3 Hz, $J_{4,5}$ = 5.9 Hz, 1H, H-4), 2.06 (m, 2H, 2H-3'), 1.80 (ddd, $J_{4,4}$ = 13.9 Hz, $J_{3,4}$ = 4.8 Hz, $J_{4,5}$ = 3.3 Hz, 1H, H-4), 1.73 - 1.57 (m, 2H, 2H-2'), 1.12 (s, 9H, Me_3C).

*4.50. (S)-5-Ethoxy-4-hydroxy-1-(4-penten-1-yl)-2-pyrrolidinone (**58g**)*

$NaBH_4$ (93 mg, 2.46 mmol) was added to a solution of imide **56** (180 mg, 982 μmol) in EtOH (7 mL) at –10 °C. After stirring at the same temperature for 1 h, the mixture was cooled to –55 °C and 1M H_2SO_4 (in EtOH, 4 mL) was added very slowly. The mixture was allowed to warm to room temperature and stirring was continued overnight. Then, the mixture was poured into saturated aqueous $NaHCO_3$ (20 mL) and the resulting mixture was extracted with CH_2Cl_2 (2x20 mL). The organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography (hexanes/EtOAc, from 3:1 to 1:3) affording **58g** as a colourless oil (185 mg, 786 μmol, 88%): $[\alpha]_D$ +29.9 (*c* 1.14, $CHCl_3$); IR (ATR) 3366, 2927, 1674, 1461, 1069, 915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddt, $J_{4',5'}$ = 17.0 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.6 Hz, 1H, H-4'), 5.05 (dq, $J_{4',5'}$ = 17.0 Hz, $J_{5',5'}$ = $J_{3',5'}$ = 1.7 Hz, 1H, H-5'), 4.99 (d, $J_{4',5'}$ = 10.2 Hz, $J_{5',5'}$ = 1.7 Hz, $J_{3',5'}$ = 1.2 Hz, 1H, H-5'), 4.70 (s, 1H; H-5), 4.22 (d, $J_{4,3}$ = 6.1 Hz, 1H, H-4), 3.64 (dq, $J_{1'',1''}$ = 9.1 Hz, $J_{1'',2''}$ = 7.1 Hz, 1H, H-1''), 3.57 (dq, $J_{1'',1''}$ = 9.1 Hz, $J_{1'',2''}$ = 7.1 Hz, 1H, H-1''), 3.49 (ddd, $J_{1',1'}$ = 13.7 Hz, $J_{1',2'}$ = 8.7 Hz, $J_{1',2'}$ = 6.7 Hz, 1H, H-1'), 3.19 (s, 1H, OH), 3.15 (ddd, $J_{1',1'}$ = 13.7 Hz, $J_{1',2'}$ = 8.7 Hz, $J_{1',2'}$ = 5.8 Hz, 1H, H-1'), 2.82 (dd, $J_{3,3}$ = 17.6 Hz, $J_{3,4}$ = 6.3 Hz, 1H, H-3), 2.26 (dd, $J_{3,3}$ = 17.6 Hz, $J_{3,4}$ = 1.3 Hz, 1H, H-3), 2.09 (q, $J_{4',3'}$ = $J_{3',2'}$ = 7.6 Hz, 2H, 2H-3'), 1.68 (m, 2H, 2H-2'), 1.24 (t, $J_{1'',2''}$ = 7.1 Hz, 3H, 3H-2''); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5 (C-2), 137.6 (C-4'), 115.1 (C-5'), 96.0 (C-5), 68.8 (C-4), 63.3 (C-1''), 40.2 (C-1'), 39.1 (C-3), 30.9 (C-3'), 26.7 (C-2'), 15.2 (C-2''); HRMS (ESI+) calcd for $[C_{11}H_{19}NO_3Na^+]$: 236.1257, found: 236.1260.

*4.51. 2,2-Dimethyl-4-(4-penten-1-yl)tetrahydro-5H-[1,3]dioxolo[4,5-b]pyrrol-5-one (**58h**)*

$NaBH_4$ (35 mg, 935 μmol) was added to a solution of imide **56** (69 mg, 374 μmol) in MeOH (1 mL) at –20 °C. After stirring at the same temperature for 2 h, the mixture was allowed to warm to room temperature. The volatiles were evaporated quickly and the residue was solved in acetone (3.5 mL) and cooled down to 0 °C. Then, conc. H_2SO_4 (350 μl, 6.4 mmol) was added very slowly. After stirring at 0 °C for 15 min, the mixture was allowed to warm to room temperature and stirred for 45 min. Then, saturated aqueous Na_2CO_3 (4 mL) was added, the volatiles were evaporated under vacuum and the aqueous phase was extracted with CH_2Cl_2 (2x5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography (hexanes/EtOAc, from 3:1 to 1:3) affording **58h** as a yellow oil (43 mg, 191 μmol, 51%): $[\alpha]_D$ +47.4 (*c* 0.91, $CHCl_3$); IR (ATR) 2932, 1691, 1431, 1373, 1235, 1216, 1072, 1026, 913 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, $J_{4',5'}$ = 17.0 Hz, $J_{4',5'}$ = 10.2 Hz, $J_{4',3'}$ = 6.6 Hz, 1H, H-4'), 5.51 (d, $J_{3a,6a}$ = 5.1 Hz, 1H, H-3a), 5.01 (dd, $J_{5',4'}$ = 17.0 Hz, $J_{5',5'}$ = 2.0 Hz, 1H, H-5'), 4.96 (dd, $J_{5',4'}$ = 10.2 Hz, $J_{5',5'}$ = 2.0 Hz, 1H, H-5'), 4.74 (td, $J_{6a,3a}$ = 5.1 Hz, $J_{6a,6}$ = 2.4 Hz, 1H, H-6a), 3.42 (ddd, $J_{1',1'}$ = 13.7 Hz, $J_{1',2'}$ = 9.2 Hz, $J_{1',2'}$ = 6.5 Hz, 1H, H-1'), 3.20 (ddd, $J_{1',1'}$ = 13.7 Hz, $J_{1',2'}$ = 9.0 Hz, $J_{1',2'}$ = 5.8 Hz, 1H, H-1'), 2.57 (m, 2H, 2H-6), 2.06 (q, $J_{3',4'}$ = $J_{3',2'}$ = 7.1 Hz, 2H, 2H-3'), 1.68 (m, 2H, 2H-2'), 1.39 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (C-5), 137.4 (C-4'), 115.1 (C-5'), 111.9 (C-2), 90.2 (C-3a), 73.1 (C-6a), 40.1 (C-1'), 37.7 (C-6), 31.1 (C-3'), 27.8 (CH_3), 26.9 (CH_3), 26.5 (C-2'); HRMS (ESI+) calcd for $[C_{12}H_{19}NO_3Na^+]$: 248.1257, found: 248.1260.

*4.52. General procedure for the cross metathesis reaction of alkenes **58a-h** with crotonaldehyde*

To a 0.3M solution of alkene **58** in dry CH_2Cl_2 at room temperature under nitrogen atmosphere was added crotonaldehyde (2 mol per mol of **58**). A 0.06 M solution of G-II catalyst in CH_2Cl_2 (0.05 mol per mol of **58**) was added to the first solution in two portions within 1 h between the two additions. After stirring at room temperature for 1 additional hour, the reaction mixture was filtered through silica gel and the silica washed with EtOAc. The organic solvent was evaporated under vacuum and the remaining oil was purified by column chromatography on silica gel.

*4.53. (E)-6-[(S)-3-Benzyloxy-2-hydroxy-5-oxopyrrolidin-1-yl]-2-hexenal, (**59a**)*

Following the general procedure, from **58a** (88 mg, 320 μmol), after column chromatography (from hexanes/EtOAc, 5:1, to EtOAc) of the crude product, **59a** was isolated as a brown oil (84 mg, 278 μmol, 87%): $[\alpha]_D$ +41.7 (*c* 0.97, $CHCl_3$); IR (ATR) 3358, 2921, 2051, 1683, 1455, 1270, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 9.48 (d, $J_{1,2}$= 7.9 Hz, 1H, H-1), 7.40 - 7.30 (m, 5H-Ar), 6.84 (dt, $J_{3,2}$ = 15.6 Hz, $J_{3,4}$ = 7.0 Hz, 1H, H-3), 6.12 (dd, $J_{2,3}$ = 15.7 Hz, $J_{2,1}$ = 7.9 Hz, 1H, H-2), 5.12 (dd, $J_{2',OH}$ = 8.2 Hz, $J_{2',3'}$ = 5.3 Hz, 1H, H-2'), 4.62 (m, 2H, ArCH_2O), 4.14 (dt, $J_{3',4'}$ = 5.8 Hz, $J_{3',2'}$ = $J_{3',4'}$ = 5.4 Hz, 1H, H-3'), 3.76 (d, $J_{OH,2'}$ = 8.2 Hz, 1H, OH), 3.38 (t, $J_{6,5}$ = 7.4 Hz, 2H, 2H-6), 2.54 (m, 2H, 2H-4'), 2.35 (q, $J_{4,3}$ = 7.3 Hz, 2H, 2H-4), 1.80 (m, 2H, 2H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9 (C-1), 171.5 (C-5'), 157.3 (C-3), 136.4 (C-Ar), 133.1 (C-2), 128.6 (C-Ar), 128.3 (C-Ar), 128.0 (C-Ar), 82.5 (C-2'), 72.1 (ArCH_2O), 71.7 (C-3'), 39.9 (C-6), 35.7 (C-4'), 30.0 (C-4), 26.2 (C-5); HRMS (ESI+) calcd for $[C_{17}H_{21}NO_4Na^+]$: 326.1368, found: 326.1363.

*4.54. (E)-6-[(S)-2-Hydroxy-3-(4-methoxybenzyl)oxy-5-oxopyrrolidin-1-yl]-2-hexenal (**59b**)*

Following the general procedure, from **58b** (330 mg, 1.08 mmol), after column chromatography (from hexanes/EtOAc, 5:1, to EtOAc) of the crude product, a mixture of two diastereoisomers of **59b** was isolated as a brown oil (320 mg, 961 μmol, 89%): IR (ATR) 3368, 2930, 1679, 1514, 1250, 1078, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 - 9.43 (m, 1H, H-1), 7.30 - 7.15 (m, 2H, 2H-Ar), 6.94 - 6.77 (m, 3H, 2H-Ar, H-3), 6.16 - 6.05 (m, 1H, H-4), 5.13 - 5.06 (m, 1H, H-2'), 4.62 - 4.44 (m, 2H, ArCH_2O), 4.12 (dt, $J_{4,3}$ = 6.3 Hz, $J_{3',2'}$ = $J_{3',4'}$ = 5.6 Hz) and 3.94 (dd, $J_{3',4'}$ = 6.2 Hz, $J_{3',4'}$ = 2.2 Hz) (1H, H-3'), 3.81 (s) and 3.79 (s) (3H, CH_3O), 3.47

(dt, $J_{6,6}$ = 14.6 Hz, $J_{6,5}$ = 7.5 Hz), 3.36 (t, $J_{6,5}$ = 7.3 Hz) and 3.24 (dt, $J_{6,6}$ = 14.6 Hz, $J_{6,5}$ = 6.8 Hz) (2H, 2H-6), 2.76 (dd, $J_{4',4'}$ = 17.5 Hz, $J_{4',3'}$ = 6.2 Hz), 2.57 - 2.45 (m), 2.39 - 2.29 (m) (4H, 2H-4', 2H-4), 1.88 - 1.71 (m, 2H, 2H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1 and 194.0 (C-1), 173.0 and 171.6 (C-5'), 159.7 and 159.4 (CH_3O*C*), 157.7 and 157.5 (C-3), 133.1 and 133.0 (C-2), 129.7 and 129.3 (C-Ar), 128.5 and 128.5 (OCH_2*C*), 114.0 and 113.9 (C-Ar), 87.6 and 82.5 (C-2'), 78.5 and 71.3 (C-3'), 71.9 and 71.1 (Ar*C*H_2O), 55.2 (*C*H_3O), 39.9 and 39.2 (C-6), 36.2 and 35.7 (C-4'), 30.0 and 29.9 (C-4), 26.2 and 25.8 (C-5); HRMS (EI) calcd for [$C_{18}H_{23}NO_5^+$]: 333.1576, found: 333.1563.

*4.55. (3S)-2-Hydroxy-5-oxo-1-[(E)-6-oxo-4-hexen-1-yl]pyrrolidin-3-yl pivalate (**59c**)*

Following the general procedure, from **58c** (78 mg, 289 µmol), after column chromatography (from hexanes/EtOAc, 5:1, to EtOAc) of the crude product, **59c** was isolated as a brown oil (74 mg, 249 µmol, 86%): $[\alpha]_D$ +17.1 (*c* 0.91, $CHCl_3$); IR (ATR) 3367, 2927, 1673, 1610, 1513, 1461, 1250, 1172 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, $J_{6',5'}$ = 7.8 Hz, 1H, H-6'), 6.87 (dt, $J_{4',5'}$ = 15.5 Hz, $J_{4',3'}$ = 6.6 Hz, 1H, H-4'), 6.14 (dd, $J_{4',5'}$ = 15.5 Hz, $J_{6',5'}$ = 7.8 Hz, 1H, H-5'), 5.33 (bd, $J_{2,3}$= 4.8 Hz, 1H, H-2), 5.16 (m, 1H, H-3), 3.78 - 3.27 (m, 3H, 2H-1', OH), 2.71 (dd, $J_{4,4}$ = 17.2 Hz, $J_{3,4}$ = 8.1 Hz, 1H, H-4), 2.60 (dd, $J_{4,4}$ = 17.2 Hz, $J_{3,4}$ = 7.0 Hz, 1H, H-4), 2.38 (q, $J_{3',4'} = J_{3',2'}$ = 7.2 Hz, 2H, 2H-3'), 1.81 (m, 2H, 2H-2'), 1.24 (s, 9H, Me_3C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9 (C-6'), 177.8 (^{t}Bu*C*O), 170.9 (C-5), 156.9 (C-4'), 133.3 (C-5'), 82.2 (C-2), 67.4 (C-3), 40.0 (C-1'), 38.8 (Me_3*C*), 34.7 (C-4), 29.9 (C-3'), 27.0 (*Me*$_3$C), 26.2 (C-2'); HRMS (ESI+) calcd for [$C_{15}H_{23}NO_5Na^+$]: 320.1468, found: 320.1476.

*4.56. (3S)-2-Hydroxy-5-oxo-1-[(E)-6-oxo-4-hexen-1-yl]pyrrolidin-3-yl benzoate (**59d**)*

Following the general procedure, from **58d** (100 mg, 346 µmol), after column chromatography (from hexanes/EtOAc, 5:1, to EtOAc) of the crude product, a mixture of two diastereoisomers of **59d** was isolated as a brown oil (91 mg, 287 µmol, 83%): IR (ATR) 3309, 2924, 1686, 1452, 1273, 1113, 1071, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, $J_{6',5'}$ = 7.8 Hz) and 9.48 (d, $J_{6',5'}$ = 7.8 Hz) (1H, H-6'), 8.06 (d, $J_{ortho,meta}$ = 7.5 Hz) and 8.01 (d, $J_{ortho,meta}$ = 7.5 Hz) (2H, 2H-Ar), 7.62 (t, $J_{meta,para}$ = 7.7 Hz) and 7.48 (t, $J_{ortho,meta} = J_{meta,para}$ = 7.5 Hz) (2H, 2H-Ar), 6.95 - 6.78 (m, 1H, H-4'), 6.09 (dd, $J_{4',5'}$ = 15.6 Hz, $J_{5',6'}$ = 7.8 Hz) and 6.05 (dd, $J_{4',5'}$ = 15.6 Hz, $J_{5',6'}$ = 7.8 Hz) (1H, H-5'), 5.52 - 5.41 (m) and 5.28 - 5.17 (m) (2H, H-2, H-3), 3.60 - 3.29 (m, 2H, 2H-1'), 3.08 (dd, $J_{4,4}$ = 18.0 Hz, $J_{4,3}$ = 7.2 Hz), 2.89 - 2.74 (m) and 2.58 (dd, $J_{4,4}$ = 18.0 Hz, $J_{4,3}$ = 1.9 Hz) (2H, 2H-4), 2.45 - 2.34 (m, 2H, 2H-3'), 1.96 - 1.74 (m, 2H, 2-H2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9 and 193.9 (C-6'), 172.1 and 171.0 (C-5), 166.4 and 165.9 (Ar*C*O), 157.1 and 157.0 (C-4'), 133.8 and 133.7 (C-5'), 133.2 and 133.2 (C-Ar), 129.7 and 129.6 (C-Ar), 128.8 (C-Ar), 128.6 and 128.5 (C-Ar), 87.3 and 82.2 (C-2), 74.7 and 68.3 (C-3), 40.1 and 39.8 (C-1'), 35.3 and 34.7 (C-4), 29.9 and 29.8 (C-3'), 26.2 and 26.0 (C-2'); HRMS (ESI+) calcd for [$C_{17}H_{19}NO_5Na^+$]: 340.1161, found: 340.1164.

*4.57. (E)-6-[(S)-3-(tert-Butyldimethylsilyloxy)-2-hydroxy-5-oxopyrrolidin-1-yl]-2-hexenal (**59e**)*

Following the general procedure, from **58e** (93 mg, 31 µmol), after column chromatography (from hexanes/EtOAc, 5:1, to EtOAc) of the crude product, **59e** was isolated as a brown oil (87 mg, 267 µmol, 86%): $[\alpha]_D$ +35.7 (*c* 1.17, $CHCl_3$); IR (ATR) 3367, 2921, 2851, 1685, 1464 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 6.84 (dt, $J_{3,2}$ = 15.6 Hz, $J_{2,4}$ = 6.8 Hz, 1H, H-3), 6.10 (dd, $J_{2,3}$ = 15.6 Hz, $J_{2,1}$ = 7.8 Hz, 1H, H-2), 5.00 (dd, $J_{2',OH}$ = 7.3 Hz, $J_{2',3'}$ = 5.3 Hz, 1H, H-2'), 4.36 (ddd, $J_{3',4'}$ = 6.8 Hz, $J_{3',2'}$ = 5.1 Hz, $J_{3',4'}$ = 4.5 Hz, 1H, H-3'), 3.66 (d, $J_{OH,2'}$ = 7.2 Hz, 1H, OH), 3.36 (m, 2H, 2H-6), 2.56 (dd, $J_{4',4'}$ = 17.1 Hz, $J_{4',3'}$ = 6.9 Hz, 1H, H-4'), 2.44 - 2.28 (m, 3H, $H_{4'}$, 2H-4), 1.80 (m, 2H, 2H-5), 0.89 (s, 9H, Me_3C), 0.12 (s, 6H, $2CH_3Si$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8 (C-1), 171.4 (C-5'), 157.2 (C-3), 133.1 (C-2), 82.9 (C-2'), 66.2 (C-3'), 39.9 (C-6), 38.8 (C-4'), 30.0 (C-4), 26.3 (C-5), 25.6 (*Me*$_3$C), 17.9 (Me$_3$*C*), –4.7 (CH_3Si), –5.2 (CH_3Si); HRMS (ESI+) calcd for [$C_{16}H_{29}NO_4SiNa^+$]: 350.1758, found: 350.1760.

*4.58. (E)-6-[(S)-3-(tert-Butyldiphenylsilyloxy)-2-hydroxy-5-oxopyrrolidin-1-yl]-2-hexenal (**59f**)*

Following the general procedure, from **58f** (1.39 g, 3.28 mmol), after column chromatography (from hexanes/EtOAc, 5:1, to EtOAc) of the crude product, a mixture of two diastereoisomers of **59e** was isolated as a brown oil (1.48 g, 3.28 mmol, quantitative): HRMS (ESI+) calcd for [$C_{26}H_{33}NO_4SiNa^+$]: 474.2071, found: 474.2075. Pure samples of each isomer were isolated by repeated chromatography. **59f*lp*** (less polar): $[\alpha]_D$ +4.7 (*c* 1.00, $CHCl_3$); IR (ATR) 3370, 2931, 2857, 1684, 1427, 1263, 1110, 974 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 7.74 - 7.55 (m, 4H-Ar), 7.54 - 7.33 (m, 6H-Ar), 6.83 (dt, $J_{3,2}$ = 15.5 Hz, $J_{3,4}$ = 6.7 Hz, 1H, H-3), 6.12 (dd, $J_{2,3}$ = 15.5 Hz, $J_{2,1}$ = 7.8 Hz, 1H, H-2), 4.93 (t, $J_{2',3'} = J_{2',OH}$ = 5.4 Hz, 1H, H-2'), 4.35 (dt, $J_{3',4'}$ = 7.3 Hz, $J_{3',4'} = J_{3',2'}$ = 5.4 Hz, 1H, H-3'), 3.78 (d, $J_{OH,2'}$ = 5.4 Hz, 1H, OH), 3.45 - 3.28 (m, 2H, 2H-6), 2.37 (dd, $J_{4',4'}$ = 17.1 Hz, $J_{4',3'}$ = 5.5 Hz, 1H, $H_{4'}$), 2.36 - 2.31 (m, 2H, 2H$_4$), 2.26 (dd, $J_{4',4'}$ = 17.1 Hz, $J_{4',3'}$ = 7.3 Hz, 1H, H-4'), 1.88 - 1.70 (m, 2H, 2H-5), 1.10 (s, 9H, Me_3C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8 (C-1), 171.6 (C-5'), 157.2 (C-3), 135.5 (C-Ar), 135.4 (C-Ar), 133.2 (C-2), 132.1 (C-Ar), 131.9 (C-Ar), 130.4 (C-Ar), 130.4 (C-Ar), 128.0 (C-Ar), 128.0 (C-Ar), 83.1 (C-2'), 67.0 (C-3'), 40.2 (C-6), 38.2 (C-4'), 30.0 (C-4), 26.8 (*Me*$_3$C), 26.4 (C-5), 19.1 (Me$_3$*C*). **59f*mp*** (more polar): $[\alpha]_D$ +35.9 (*c* 1.92, $CHCl_3$); IR (ATR) 3370, 2931, 2857, 1683, 1427, 1263, 1111, 974 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 7.73 - 7.58 (m, 4H, 4H-Ar), 7.50 - 7.33 (m, 6H, 6H-Ar), 6.84 (dt, $J_{3,2}$ = 15.5 Hz, $J_{3,4}$ = 6.6 Hz, 1H, H-3), 6.09 (dd, $J_{2,3}$ = 15.5 Hz, $J_{2,1}$ = 7.8 Hz, 1H, H-2), 4.93 (s, 1H, H-2'), 4.18 (dd, $J_{3',4'}$ = 6.1 Hz, $J_{3',4'}$ = 1.9 Hz, 1H, H-3'), 3.71 (s, 1H, OH), 3.46 (dt, $J_{6,6}$ = 14.3 Hz, $J_{6,5}$ = 7.2 Hz, 1H, H-6), 3.17 (dt, $J_{6,6}$ = 14.3 Hz, $J_{6,5}$ = 6.3 Hz, 1H, H-6), 2.58 (dd, $J_{4','4}$ = 17.3 Hz, $J_{4',3'}$ = 6.1 Hz, 1H, H-4'), 2.35 (q, $J_{4,3} = J_{4,5}$ = 6.9 Hz, 2H, 2H-4), 2.24 (dd, $J_{4',4'}$ = 17.3 Hz, $J_{4',3'}$ = 1.9 Hz, 1H, H-4'), 1.76 (m, 2H, 2H-5), 1.07 (s, 9H, Me_3C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0 (C-1), 173.4 (C-5'), 157.5 (C-3), 135.5 (C-Ar), 133.1 (C-2), 132.8 (C-Ar), 130.1 (C-Ar), 127.8 (C-Ar), 89.7 (C-2'), 73.3 (C-3'), 39.1 (C-6), 38.9 (C-4'), 29.7 (C-4), 26.7 (*Me*$_3$C), 25.9 (C-5), 19.0 (Me$_3$*C*).

*4.59. (E)-6-[(S)-2-Ethoxy-3-hydroxy-5-oxopyrrolidin-1-yl]-2-hexenal (**59g**)*

Following the general procedure, from **58g** (242 mg, 1.13 mmol), after column chromatography (from hexanes/EtOAc, 3:1, to EtOAc) of the crude product, **59g** was isolated as a brown oil (235 mg, 1.03 mmol, 91%): $[\alpha]_D$ +37.5 (*c* 1.04, $CHCl_3$); IR (ATR) 3397, 2928, 1682, 1459, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 6.86 (dt, $J_{3,2}$ = 15.4 Hz, $J_{3,4}$ = 6.7 Hz, 1H, H-3), 6.09 (dd, $J_{2,3}$ = 15.4 Hz, $J_{2,1}$ = 7.9 Hz, 1H, H-2), 4.65 (s, 1H, H-2'), 4.19 (d, $J_{3',4'}$ = 6.0 Hz, 1H, H-3'), 3.60 (dq, $J_{1'',1''}$ = 9.1 Hz, $J_{1'',2''}$ = 7.1 Hz, 1H, H-1''), 3.53 (dq, $J_{1'',1''}$ = 9.1 Hz, $J_{1'',2''}$ = 7.1 Hz, 1H, H-1''), 3.44 (dt, $J_{6,6}$ = 14.6 Hz, $J_{6,5}$ = 7.4 Hz, 1H, H-6), 3.21 (dt, $J_{6,6}$= 14.6 Hz, $J_{6,5}$ = 6.8 Hz, 1H, H-6), 2.76 (dd, $J_{4',4'}$ = 17.5 Hz, $J_{3',4'}$ = 6.0 Hz, 1H, H-4'), 2.35 (q, $J_{4,3} = J_{4,5}$ = 6.8 Hz, 2H, 2H-4), 2.22 (d, $J_{4',4'}$ = 17.5 Hz, 1H, H-4'), 1.68 (m, 2H, 2H-5), 1.19 (t, $J_{1'',2''}$ = 7.0 Hz, 3H, 3H-2''); ^{13}C NMR (100 MHz, $CDCl_3$) δ

194.3 (C-1), 174.1 (C-5'), 157.9 (C-3), 133.0 (C-2), 96.1 (C-2'), 68.3 (C-'3), 63.2 (C-1''), 40.0 (C-6), 38.9 (C-4'), 29.8 (C-4), 25.9 (C-5), 15.2 (C-2''); HRMS (ESI+): calcd for $[C_{12}H_{19}NO_4Na^+]$: 264.1212, found: 264.1205.

4.60. *(E)-6-(2,2-Dimethyl-5-oxotetrahydro-4H-[1,3]dioxolo[4,5-b]pyrrol-4-yl)-2-hexenal (**59h**)*

Following the general procedure, from **58h** (10 mg, 44 μmol), after column chromatography (from hexanes/EtOAc, 3:1, to EtOAc) of the crude product, **59h** was isolated as a brown oil (9 mg, 36 μmol, 82%): $[\alpha]_D$ +50.1 (*c* 0.91, $CHCl_3$); IR (ATR) 2921, 2852, 1690, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 6.85 (dt, $J_{3,2}$ = 15.7 Hz, $J_{3,4}$ = 6.7 Hz, 1H, H-3), 6.13 (dd, $J_{2,3}$ = 15.7 Hz, $J_{2,1}$ = 7.8 Hz, 1H, H-2), 5.51 (d, $J_{6a',3a'}$ = 7.8 Hz, 1H, H-6a'), 4.77 (td, $J_{3a',6a'}$ = 5.2 Hz, $J_{3a'4'}$ = 2.8 Hz 1H, H-3a'), 3.37 (m, 2H, 2H-6), 2.61 (m, 2H, 2H-4'), 2.37 (q, $J_{4,5} = J_{4,3}$ = 6.8 Hz, 2H, 2H-4), 1.84 (m, 2H, 2H-5), 1.41 (s, 3H, CH_3), 1.39 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8 (C-1), 171.6 (C-5'), 156.8 (C-3), 133.2 (C-2), 112.1 (C-2'), 90.4 (C-6a'), 73.1 (C-3a'), 40.1 (C-6), 37.6 (C-4'), 30.0 (C-4), 27.8 (CH_3), 26.8 (CH_3), 25.9 (C-5); HRMS (ESI+) calcd for $[C_{13}H_{19}NO_4Na^+]$: 276.1212, found: 276.1201.

4.61. *General procedure for the Morita-Baylis-Hillman Cyclization*

To a 0.1M solution of α,β-unsaturated aldehyde **59** in dry CH_3CN at –35 ºC under nitrogen atmosphere, were added Me_2S (1.5 mol per mol of aldehyde) and TESOTf (2.5 mol per mol of aldehyde) in this strict order. The resulting mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (the same amount as CH_3CN). After evaporation of CH_3CN under vacuum, the resulting residue was extracted twice with CH_2Cl_2 (the same volume as CH_3CN), the organic extracts dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel.

4.62. *(1S,9aRS)-1-Benzyloxy-3-oxo-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carbaldehyde (**60a**)*

Following the general procedure, from **59a** (129 mg, 425 μmol), after column chromatography (from hexanes/EtOAc, 2:1, to EtOAc) of the crude product, a mixture of two diastereoisomers of **60a** was isolated as a brown oil (36 mg, 128 μmol, 30%): IR (ATR) 2925, 1674, 1454, 1216, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.42 (bs, 1H, CHO), 7.44 - 7.11 (m, 5H, 5H-Ar), 7.00 (bt, $J_{8,7}$ = 7.1 Hz) and 6.95 (bt, $J_{8,7}$ = 7.1 Hz) (1H, H-8), 4.84 - 4.13 (m, 5H, H-1, H-5, H 9a, ArCH_2O), 3.05 - 2.27 (m, 5H, H-5, 2H-7, 2H-2), 2.23 - 2.10 (m, 1H, H-6), 1.85 - 1.73 (m, 1H, H-6); HRMS (ESI+) calcd for $[C_{17}H_{19}NO_3Na^+]$: 308.1257, found: 308.1253.

4.63. *(1S,9aRS)-9-Formyl-3-oxo-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-1-yl pivalate (**60c**)*

Following the general procedure, from **59c** (38 mg, 128 μmol), after column chromatography (from hexanes/EtOAc, 2:1, to EtOAc) of the crude product, a mixture of two diastereoisomers of **60c** was isolated as a brown oil (20 mg, 72 μmol, 56%): IR (ATR) 2925, 1709, 1400, 1281, 1146 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.42 (s), and 9.38 (s) (1H, CHO), 7.01 (dd, $J_{8,7}$ = 8.3 Hz, $J_{8,7}$ = 6.0 Hz) and 6.97 (ddd, $J_{8,7}$ = 8.3 Hz, $J_{8,7}$ = 6.0 Hz, *J* = 1.2 Hz) (1H, H-8), 5.51 (dd, $J_{1,2}$ = 5.7 Hz, $J_{1,9a}$ = 5.1 Hz) and 5.31 (dt, $J_{1,2}$ = 7.3 Hz, $J_{1,9a} = J_{1,2}$ = 3.2 Hz) (1H, H-1), 4.92 (bd, $J_{1,9a}$ = 5.1 Hz) and 4.66 (bs) (1H, H-9a), 4.33 - 4.14 (m, 1H, H-5), 2.97 (dt, *J* = 14.3 Hz, *J* = 7.2 Hz), 2.90 - 2.74 (m) and 2.57 - 2.35 (m) (5H, 2H-2, H-5, 2H-7), 2.18 (m) and 1.81 (m) (1H, H-6), 1.24 (s, 9H, Me_3C); HRMS (ESI+) calcd for $[C_{15}H_{21}NO_4Na^+]$: 302.1363, found: 302.1366.

4.64. *(1S,9aRS)-9-Formyl-3-oxo-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-1-yl benzoate (**60d**)*

Following the general procedure, from **59d** (45 mg, 142 μmol), after column chromatography (from hexanes/EtOAc, 2:1, to EtOAc) of the crude product, a mixture of two diastereoisomers of **60d** was isolated as a brown oil (27 mg, 90 μmol, 63%): IR (ATR) 2921, 2850, 1719, 1685, 1452, 1274, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.45 (s) and 9.36 (s) (1H, CHO), 8.06 (d, $J_{ortho,meta}$ = 7.5 Hz) and 7.90 (d, $J_{ortho,meta}$ = 7.5 Hz) (2H, 2H-Ar), 7.61 - 7.54 (m, 1H, H-Ar), 7.50 - 7.41 (m, 2H, 2H-Ar), 7.04 - 6.97 (m, 1H, H-8), 5.82 (t, $J_{1,2} = J_{1,9a}$ = 4.9 Hz) and 5.61 (dt, $J_{1,2}$ = 7.0 Hz, $J_{1,9a} = J_{1,2}$ = 2.8 Hz) (1H, H-1), 5.03 (bd, $J_{9a,1}$ = 4.9 Hz) and 4.84 (bs) (1H, H-9a), 4.34 - 4.19 (m, 1H, H-5), 3.07 - 2.82 (m) and 2.55 - 2.33 (m) (5H, 2H-2, H-5, 2H-7), 2.65 (d, $J_{2,2}$ = 17.7 Hz) and 2.59 (dd, $J_{2,2}$ = 18.1 Hz, $J_{2,1}$ = 2.8 Hz) (1H, H-2), 2.20 (m) and 1.84 (m) (1H, H-6); HRMS (ESI+) calcd for $[C_{17}H_{17}NO_4Na^+]$: 322.1050, found: 322.1049.

4.65. *(1S,9aS)-1-(tert-Butyldiphenylsilyl)oxy-3-oxo-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carbaldehyde (**60f**)*

Following the general procedure, from **59f** (1.23 g, 2.72 mmol), after column chromatography (from hexanes/EtOAc, 2:1, to EtOAc) of the crude product, **60f** was isolated as a pale yellow solid (800 mg, 1.85 mmol, 68%): Mp 95-98 ºC (hexanes/Et_2O); $[\alpha]_D$ +63.2 (*c* 1.08, $CHCl_3$); IR (ATR) 2931, 2857, 1679, 1427, 1220, 1179, 1105, 1065, 939 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H, CHO), 7.61 - 7.52 (m, 4H, 4H-Ar), 7.47 - 7.36 (m, 6H, 6H-Ar), 7.01 (dd, $J_{8,7}$ = 8.4 Hz, $J_{8,7}$ = 5.8 Hz, 1H, H-8), 4.68 (bd, $J_{9a,1}$ = 4.5 Hz, 1H, H-9a), 4.62 (t, $J_{1,2} = J_{1,9a}$ = 6.5 Hz, 1H, H-1), 4.15 (dd, $J_{5,5}$ = 14.2 Hz, $J_{5,6}$ = 7.8 Hz, 1H, H-5), 3.08 (m, 1H, H-7), 2.76 (ddd, $J_{5,5}$ = 14.3 Hz, $J_{5,6}$ = 10.8 Hz, $J_{5,6}$ = 6.9 Hz, 1H, H-5), 2.44 - 2.39 (m, 1H, H-7), 2.36 (dd, $J_{2,2}$ = 17.2 Hz, $J_{2,1}$ = 4.5 Hz, 1H, H-2), 2.25 (m, 1H, H-6), 2.27 (d, $J_{2,2}$ = 17.2 Hz, 1H, H-2), 1.80 (m, 1H, H-6), 0.99 (s, 9H, Me_3C); ^1H NMR (400 MHz, C_6D_6) δ 9.20 (s, 1H, CHO), 7.78 - 7.62 (m, 4H, 4H-Ar), 7.36 - 7.29 (m, 6H, 6H-Ar), 6.26 (dd, $J_{8,7}$ = 8.5 Hz, $J_{8,7}$ = 5.9 Hz, 1H, H-8), 4.60 (t, $J_{1,2} = J_{1,9a}$ = 4.7 Hz, 1H, H-1), 4.43 (bd, $J_{9a,1}$ = 4.5 Hz, 1H, H-9a), 4.12 (dd, $J_{5,5}$ = 14.0 Hz, $J_{5,6}$ = 7.1 Hz, 1H, H-5), 2.90 (m, 1H, H-7), 2.32 (d, $J_{2,2}$ = 16.9 Hz, 1H, H-2), 2.24 (ddd, $J_{5,5}$ = 14.0 Hz, $J_{5,6}$ = 10.7 Hz, $J_{5,6}$ = 6.7 Hz, 1H, H-5), 2.01 (m, 1H, H-6), 1.93 (dd, $J_{2,2}$ = 16.9 Hz, $J_{2,1}$ = 5.1 Hz, 1H, H-2), 1.81 (m, 1H, H-7), 1.25 (m, 1H, H-6), 1.12 (s, 9H, Me_3C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9 (CHO), 172.6 (C-3), 154.9 (C-8), 140.2 (C-9), 135.9 (C-Ar), 135.7 (C-Ar), 133.2 (C-Ar), 132.2 (C-Ar), 130.0 (C-Ar), 129.9 (C-Ar), 127.7 (C-Ar), 127.7 (C-Ar), 69.4 (C-1), 64.8 (C-9a), 41.0 (C-2), 37.9 (C-5), 26.8 (*Me*$_3$C), 23.8/23.6 (C-6/C-7), 19.1 (Me$_3$*C*); ^{13}C NMR (100 MHz, C_6D_6) δ 192.2 (CHO), 171.1 (C-3), 153.5 (C-8), 140.7 (C-9), 136.0 (C-Ar), 135.8 (C-Ar), 133.7 (C-Ar), 132.5 (C-Ar), 129.9 (C-Ar), 129.9 (C-Ar), 127.8 (C-Ar), 127.8 (C-Ar), 69.7 (C-1), 64.3 (C-9a), 40.5 (C-2), 37.5 (C-5), 26.7 (*Me*$_3$C), 23.8/23.7 (C-6/C-7), 19.0 (Me$_3$*C*); HRMS (ESI+) calcd for $[C_{26}H_{31}NO_3SiNa^+]$: 456.1965, found: 456.1973.

4.66. *Methyl (E)-3-(3-oxo-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-9-yl)acrylate (**66**)*

In a schlenk vessel, aldehyde **51** (106 mg, 0.59 mmol) was dissolved in dry THF (5 mL) under nitrogen atmosphere and cooled down to 0 ºC. Sodium hydride (60% in wt, 24 mg, 0.59 mmol) and a solution of methyl 2-(dimethoxyphosphoryl)acetate (95 μL, 0.59 mmol) in dry THF (4 mL) were added successively and the mixture was allowed to warm to room temperature and stirred overnight. Then, the reaction was quenched with saturated

aqueous NH_4Cl (15 mL) and diluted with Et_2O (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3x10 mL), the organic fractions were combined, washed with 5% aqueous NaOH (3x15 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Ester **66** was isolated as a pale yellow syrup (135 mg, 0.57 mmol, 98%): R_f 0.18 (EtOAc); IR (ATR) 3368, 2929, 2856, 1662, 1623, 1435, 1420, 1266, 1195, 1163 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.19 (d, $J_{2,3}$ = 16.2 Hz, 1H, H-3), 6.23 (dd, $J_{8',7'}$ = 9.1 Hz, $J_{8',7'}$ = 5.8 Hz, 1H, H-8'), 5.73 (d, $J_{2,1}$ = 16.2 Hz, 1H, H-2), 4.47 (m, 1H, H-9a'), 4.11 (ddd, $J_{5',5'}$ = 14.0 Hz, $J_{5',6'}$ = 8.9 Hz, $J_{5',6'}$ = 2.9 Hz, 1H, H-5'), 3.75 (s, 3H, OCH_3), 2.89 (dt, J_{gem} = 14.0 Hz, $J_{5',6'}$ = 8.5 Hz, 1H, H-5'), 2.43 (m, 4H, H-1', H-7', 2H-2'), 2.13 (m, 2H, H-6', H-7'), 1.87 (m, 1H, H-6'), 1.71 (m, 1H, H-1'); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.7 (C-3'), 167.4 (C-1), 146.1 (C-3), 140.2 (C-8'), 139.2 (C-9'), 116.2 (C-2), 61.4 (C-9a'), 51.8 (CH_3), 38.9 (C-5'), 30.3 (C-2'), 26.4 (C-1'), 24.4 (C-6'), 23.2 (C-7'); HRMS (ESI+) calcd for [$C_{13}H_{17}NO_3Na^+$]: 258.1101, found: 258.1107.

4.67. *(E)-9-(3-Hydroxyprop-1-en-1-yl)-5,6,7,9a-tetrahydro-1H-pyrrolo[1,2-a]azepin-3(2H)-one (**67**)*

DIBAL-H (1M in toluene, 470 µL, 0.47 mmol) was added to a solution of ester **66** (44 mg, 0.19 mmol) in dry CH_2Cl_2 (1.5 mL) at –78 °C under nitrogen atmosphere and the mixture was stirred overnight at this temperature. Then, the reaction was quenched with MeOH (1 mL), followed by the addition of a saturated aqueous solution of Rochelle's salt (4 mL). The resulting mixture was allowed to warm to room temperature and stirred until aluminium salts were dissolved. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (4x10 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc) to furnish **67** as a yellowish syrup (14.5 mg, 0.70 mmol, 37%): R_f 0.14 (EtOAc/MeOH, 9:1); IR (ATR) 3368, 2929, 2856, 1662, 1623, 1435, 1420, 1266, 1195, 1163, cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.12 (d, $J_{1',2'}$ = 16.1 Hz, 1H, H-1'), 5.81 (dd, $J_{8,7}$ = 9.1 Hz, $J_{8,7}$ = 5.7 Hz, 1H, H-8), 5.65 (dt, $J_{2',1'}$ = 16.1 Hz, $J_{2',3'}$ = 5.8 Hz, 1H, H-2'), 4.47 (m, 1H, H-9a), 4.19 (bd, $J_{3',2'}$ = 5.5 Hz, 2H, 2H-3'), 4.05 (ddd, J_{gem} = 13.8 Hz, $J_{5,6}$ = 8.9 Hz, $J_{5,6}$ = 2.3 Hz, 1H, H-5), 2.88 (dt, J_{gem} = 13.8 Hz, $J_{5,6}$ = 8.5 Hz, 1H, H-5), 2.49 - 2.24 (m, 4H, H-1, H-7, 2H-2), 2.14 - 1.82 (m, 3H, H-1, H-6, H-7), 1.67 (m, 1H, H-6); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.9 (C-3), 139.4 (C-9), 132.7 (C-1'), 131.0 (C-8), 126.5 (C-2'), 63.7 (C-3'), 62.0 (C-9a), 38.9 (C-5), 30.5 (C-2), 26.6 (C-1), 24.7 (C-6), 22.4 (C-7); HRMS (ESI+) calcd for [$C_{12}H_{17}NO_2Na^+$]: 230.1157, found: 230.1139.

4.68. *(E)-3-(3-Oxo-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-9-yl)-2-propenal (**68**)*

Method A: A commercially available solution of DMPI in CH_2Cl_2 (15% wt, 250 µL, 0.12 mmol) was added via syringe to a solution of alcohol **67** (20 mg, 0.10 mmol) in dry CH_2Cl_2 (1 mL) at room temperature under nitrogen atmosphere. After stirring for 1 h at room temperature, TLC analysis (EtOAc/MeOH, 10:1) indicated the complete consumption of the starting material. The reaction was quenched with 500 µL of a solution prepared by addition of $Na_2S_2O_3$ (17 g) to saturated aqueous $NaHCO_3$ (90 mL) and the mixture was stirred for 15 min. The aqueous phase was extracted with CH_2Cl_2 (2x2 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Column chromatography (EtOAc) of the resulting oil provided aldehyde **68** as a white solid (15.4 mg, 0.08 mmol, 78%).

Method B: A solution of borane dimethylsulfide (10M in THF, 167 µL, 1.67 mmol) in dry THF (1.2 mL) was added dropwise to a solution of ethoxyacetylene (40% wt in hexanes, 2 mL, 8.36 mmol) in dry THF (1.2 mL) under nitrogen atmosphere at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. Then, it was heated at 60 °C for 1 h. After cooling down the reaction mixture to room temperature, the volatiles were removed under reduced pressure. The brown residue was dissolved in dry toluene (5.8 mL) and cooled to –78 °C. Then, Et_2Zn (1M in hexanes, 5.9 mL, 5.85 mmol) was added dropwise and the mixture was stirred for 20 min at this temperature before the addition in one portion of aldehyde **51** (599 mg, 3.34 mmol). The mixture was allowed to warm up to room temperature, very slowly, and stirred overnight. Then, the reaction mixture was cooled to 0 °C, diluted with Et_2O (6 mL) and carefully treated with brine (6 mL). After that, the mixture was vigorously stirred for 5 min before the dropwise addition of 2M HCl until pH < 4. The mixture was stirred for another 10 min controlling their evolution by TLC (alumina, EtOAc). Then, the aqueous layer was extracted with Et_2O (3x20 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (20 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on neutral alumina (EtOAc) to furnish **68** as a white solid (483 mg, 2.35 mmol, 70%): R_f 0.34 (EtOAc/MeOH, 10:1); IR (ATR) 2949, 2927, 2866, 1667, 1621, 1454, 1425, 1413, 1131, 982 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.48 (d, $J_{3,2}$ = 7.6 Hz, 1H, H-1), 6.96 (d, $J_{1,2}$ = 16.2 Hz, 1H, H-3), 6.33 (dd, $J_{8',7'}$ = 9.2 Hz, $J_{8',7'}$ = 5.6 Hz, 1H, H-8'), 5.98 (dd, $J_{2,1}$ = 16.2 Hz, $J_{2,1}$ = 7.6 Hz, 1H, H-2), 4.46 (t, $J_{9a,1}$ = 6.8 Hz, 1H, H-9a'), 4.08 (ddd, J_{gem} = 14.0 Hz, $J_{5',6'}$ = 8.9 Hz, $J_{5',6'}$ = 3.0 Hz, 1H, H-5'), 2.88 (dt, J_{gen} = 14.0 Hz, $J_{5',6'}$ = 8.4 Hz, 1H, H-5'), 2.41 (m, 4H, H-1', H-7', 2H-2'), 2.13 (m, 2H, H-6', H-7'), 1.84 (m, 1H, H-6'), 1.72 (m, 1H, H-1'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6 (C-1), 174.5 (C-3'), 153.6 (C-3), 142.3 (C-8'), 139.6 (C-9'), 127.1 (C-2), 61.1 (C-9a'), 38.6 (C-5'), 30.0 (C-2'), 26.1 (C-1'), 24.1 (C-6'), 23.2 (C-7'); HRMS (ESI+) calcd for [$C_{12}H_{15}NO_2Na^+$]: 228.0995, found: 228.0989.

4.69. *Methyl (E)-3-(3-oxooctahydro-1H-pyrrolo[1,2-a]azepin-9-yl)acrylate (**69**)*

In a schlenk vessel, aldehyde **62** (300 mg, 1.66 mmol) was dissolved in dry THF (25 mL) under nitrogen atmosphere and cooled down to 0 °C. Sodium hydride (60% in wt, 66 mg, 1.66 mmol) and methyl 2-(dimethoxyphosphoryl)acetate (268µL, 1.66 mmol) were added successively and the mixture was allowed to warm to room temperature and stirred overnight. Then, the reaction was quenched with saturated aqueous NH_4Cl (15 mL) and the mixture extracted with Et_2O (3x15 mL). The organic fractions were combined and washed with 5% aqueous NaOH (3x15 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexanes/EtOAc, 4:1) affording a 5:3 mixture of two *E* diastereoisomers of **69** (223 mg, 0.94 mmol, 57%) and a 5:1 mixture of two *Z* diastereoisomers (134 mg, 0.56 mmol, 34%) as pale yellow syrups. Repeated chromatography lead to the isolation of an analytical sample of the major isomer of **69**: R_f 0.38 (EtOAc/MeOH, 9:1); IR (ATR) 2928, 2855, 2363, 1719, 1673, 1434, 1420, 1315, 1276, 1194, 1178, 1152, 1035, 987 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.84 (dd, $J_{3,2}$ = 15.7 Hz, $J_{3,9'}$ = 8.5 Hz, 1H, H-3), 5.90 (dd, $J_{2,3}$ = 15.7 Hz, $J_{2,9'}$ = 1.1 Hz 1H, H-2), 3.91 (ddd, $J_{9a',1'}$ = 8.5 Hz, $J_{9a',9'}$ = 6.9 Hz, $J_{9a',1'}$ = 4.6 Hz, 1H, H-9a'), 3.76 (m, 4H, H-5', OCH_3), 3.08 (ddd, J_{gem} = 13.9 Hz, $J_{5',6'}$ = 8.3 Hz, $J_{5',6'}$ = 3.3 Hz, 1H, H-5'), 2.71 (m, 1H, H-9'), 2.34 (d, J_{gem} = 9.9 Hz, 1H, H-2'), 2.33 (dd, J_{gem} = 9.9 Hz, $J_{2',1'}$ = 3.1 Hz, 1H, H-2'), 1.98 (m, 1H, H-1'), 1.65 (m, 7H, H-1', 2H-6', 2H-7', 2H-'8); ^{13}C NMR (90.0 MHz, $CDCl_3$) δ 175.0 (C-3'), 166.6 (C-1), 147.2 (C-3), 122.9 (C-2), 61.4 (C-9a'), 51.8 (CH_3), 46.4 (C-9'), 42.5 (C-5'), 30.7 (C-2'), 29.8 (C-8'), 28.2 (C-7'), 27.8 (C-6'), 23.1 (C-1');

HRMS (ESI+) calcd for $[C_{13}H_{19}NO_3H^+]$: 238.1438, found: 238.1431.

4.70. *(E)-9-(3-Hydroxyprop-1-en-1-yl)hexahydro-1H-pyrrolo[1,2-a]azepin-3(2H)-one (**70**) and (E)-3-(Octahydro-1H-pyrrolo[1,2-a]azepin-9-yl)prop-2-en-1-ol (**71**)*

In a schlenk vessel ester **69** (165 mg, 0.70 mmol) was solved in dry CH_2Cl_2 (6 mL) and the resulting solution was cooled down to –78 °C under nitrogen atmosphere. A solution of DIBAL-H (1M in toluene, 1.7 mL, 1.74 mmol) was added dropwise and the mixture was stirred overnight at the same temperature. Then, the reaction was quenched with MeOH followed by the addition of a saturated aqueous solution of Rochelle's salt. The mixture was allowed to warm to room temperature and stirred until the aluminium salts were dissolved. The layers were separated and the aqueous one was extracted with CH_2Cl_2 (4x10 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc) to recover ester **69** (50 mg, 0.21mmol, 30%) and to furnish a mixture of two diastereoisomers of amine **71** (28 mg, 0.14 mmol, 21%) and a mixture of two diastereoisomers of lactam **70** (46 mg, 0.22 mmol, 32%) as yellowish syrups.

70: R_f 0.24 (EtOAc/MeOH, 9:1); IR (ATR) 3370, 2925, 2855, 1656, 1438, 1423, 910 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, major isomer) δ 5.75 (dt, $J_{2',1'}$ = 15.4 Hz, $J_{2',3'}$ = 5.3 Hz, 1H, H-2'), 5.59 (bdd, $J_{1',2'}$ = 15.4 Hz, $J_{1',9}$ = 8.4 Hz, 1H, H-1'), 4.12 (dd, $J_{3',2'}$ = 5.6 Hz, $J_{3',1'}$ = 0.8 Hz, 2H, 2H-3'), 3.85 (td, $J_{9a,9}$ = 7.6 Hz ≈ $J_{9a,1}$, $J_{9a,1}$ = 4.1 Hz, 1H, H-9a), 3.64 (m, 1H, H-5), 3.15 (m, 1H, H-5), 2.53 (m, 1H, H-9), 2.33 (d, $J_{2,2}$ = 9.6 Hz, 1H, H-2), 2.31 (dd, J_{gem} = 9.6 Hz, $J_{2,1}$ = 2.1 Hz, 1H, H-2), 1.98 (m, 1H, H-1), 1.64 (m, 7H, H-1, 2H-6, 2H-7, 2H-8); ^{13}C NMR (62.5 MHz, $CDCl_3$, major isomer) δ 175.3 (C-3), 131.7 (C-2'), 130.6 (C-1'), 63.6 (C-3'), 62.1 (C-9a), 46.7 (C-9), 42.9 (C-5), 31.3/30.9/28.0/ 27.6/23.2 (C-1/C-2/C-6/C-7/C-8); HRMS (ESI+) calcd for $[C_{12}H_{19}NO_2Na^+]$: 232.1308, found: 232.1312.

71: R_f 0.16 (EtOAc:MeOH, 9:1); ^1H NMR (250 MHz, $CDCl_3$, major isomer) δ 5.90 (bdd, $J_{2,3}$ = 15.4 Hz, $J_{2,1}$ = 8.9 Hz, 1H, H-2), 5.66 (dt, $J_{3,2}$ = 15.4 Hz, $J_{3,9'}$ = 5.6 Hz, 1H, H-3), 4.12 (dd, $J_{1,2}$ = 5.6 Hz, $J_{1,3}$ = 1.2 Hz, 2H, 2H-1), 3.19 (m, 2H, H-5', H-9a'), 2.94 (m, 1H, H-9'), 2.60 - 1.40 (m, 13H, 2H-1', 2H-2', 2H-3', H-5', 2H-6', 2H-7', 2H-8').

4.71. *(E)-3-(3-Oxooctahydro-1H-pyrrolo[1,2-a]azepin-9-yl)prop-2-enal (**72**)*

A commercially available solution of the DMPI in CH_2Cl_2 (15% wt, 250 µL, 120 µmol) was added via syringe to a solution of alcohol **71** (20 mg, 100 µmol) in dry CH_2Cl_2 (1 mL) under nitrogen atmosphere at room temperature. After stirring 1 h at room temperature, TLC analysis (EtOAc/MeOH, 10:1) indicated the complete consumption of the starting material. The solution was quenched with 200 µL of a solution prepared by addition of $Na_2S_2O_3$ (17 g) to saturated aqueous $NaHCO_3$ (90 mL) and the mixture was stirred for 15 min. The aqueous phase was extracted with CH_2Cl_2 (2x2 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. Column chromatography (EtOAc) of the resulting oil provided aldehyde **72** as a yellow syrup (12 mg, 60 µmol, 61%): R_f 0.20 (EtOAc/MeOH, 10:1); ^1H NMR (250 MHz, $CDCl_3$) δ 9.53 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1), 6.73 (dd, $J_{3,2}$ = 15.7 Hz, $J_{3,9'}$ = 8.2 Hz, 1H, H-3), 6.20 (ddd, $J_{2,3}$ = 15.7 Hz, $J_{2,1}$ = 7.7 Hz, $J_{2,9'}$ = 1.0 Hz, 1H, H-2), 3.98 (ddd, $J_{9a',1'}$ = 8.1 Hz, $J_{9a',9'}$ = 7.4 Hz, $J_{9a',1'}$ = 4.3 Hz, 1H, H-9a'), 3.72 (m, 1H, H-5'), 3.16 (m, 1H, H-5'), 2.85 (m, 1H, H-9'), 2.36 (dd, J_{gem} = 9.8 Hz, $J_{2',1'}$ = 6.3 Hz, 2H, 2H-2'), 2.12 - 1.55 (m, 8H, 2H-1', 2H-6', 2H-7', 2H-8'). This product was very unstable and could not be fully characterized.

4.72. *3-(3-Oxo-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-9-yl)-3-(5-oxo-2,5-dihydrofuran-2-yl)propanal (**73**)*

A solution of aldehyde **68** (80 mg, 390 µmol) in CH_2Cl_2 (400 µL) was added to a solution of pyrrolidine (6.5 µL, 78 µmol), DNBA (16.5 mg, 78 µmol) and H_2O (14 µL, 780 µmol) in CH_2Cl_2 (2 mL) at –20 °C. The mixture was stirred for 5 min before the addition of furane **39** (100 µL, 585 µmol) and then overnight at –20 °C. After this time, the mixture was warmed gradually, during 24 h, to room temperature. When TLC analysis (EtOAc/MeOH, 10:1) showed the total consumption of **39**, the solution was directly submitted to column cromatography (from EtOAc to EtOAc/MeOH, 10:1) to recover aldehyde **39** (18.7 mg, 91 µmol, 23%) and furnish a diastereoisomeric mixture of **73** as a yellowish syrup (79 mg, 273 µmol, 70%): R_f 0.34 (EtOAc/MeOH, 10:1); IR (ATR) 3349, 2920, 2851, 2362, 1742, 1656, 1459, 1263, 1162, 1097, 1034 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$, major isomer) δ 9.75 (m, 1H, H-1), 7.46 (m, 1H, H-3''), 6.23 (m, 1H, H-4''), 5.77 (m, 1H, H-8'), 5.10 (m, 1H, H-2''), 4.32 (m, 1H, H-9a'), 4.04 (m, 1H, H-5'), 2.89 (m, 4H, H-3, H-5', 2H-2), 2.37 (m, 4H, H-1', H-7', 2H-2'), 1.97 (m, 2H, H-6', H-7'), 1.66 (m, 2H, H-6', H-1'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1 - 198.7 (C-1), 174.4 (C-3'), 171.9 (C-5''), 154.1 - 153.6 (C-3''), 139.0 (C-9'), 128.3 - 127.8 (C-8'), 123.3 - 123.0 (C-4''), 84.4 - 83.5 (C-2''), 65.2 - 64.6 (C-9a'), 44.8 - 43.5 (C-2), 40.0 - 38.1 (C-3, C-5'), 30.6 - 21.7 (C-1', C-2', C-6', C-7'); HRMS (ESI+) calcd for $[C_{16}H_{19}NO_4Na^+]$: 312.1206, found: 312.1199.

4.73. *9-[2-(1,3-Dithiolan-2-yl)-1-(5-oxo-2,5-dihydrofuran-2-yl)ethyl]-5,6,7,9a-tetrahydro-1H-pyrrolo[1,2-a]azepin-3(2H)-one (**74**)*

1,2-Ethanedithiol (38 µL, 455 µmol) and $BF_3{\cdot}Et_2O$ (58 µL, 455 µmol) were added to a solution of aldehyde **73** (110 mg, 380 µmol) in dry CH_2Cl_2 (5.5 mL) at –15 °C and the mixture was stirred for 1 h. When TLC analysis (EtOAc/MeOH, 10:1) showed the total consumption of the aldehyde, the mixture was treated with H_2O (8 mL) and warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x12 mL) and the combined organic extracts were washed with brine (12 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc) to furnish a diastereoisomeric mixture of **74** as a yellowish syrup (78 mg, 213 µmol, 56%): R_f 0.36 (EtOAc/MeOH, 10:1); IR (ATR) 3426, 2926, 2360, 1748, 1668, 1418, 1366, 1323, 1264, 1162, 1098, 1035 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, major isomer) δ 7.48 (dd, $J_{3'',4''}$ = 5.7 Hz, $J_{3'',2''}$ = 1.3 Hz 1H, H-3''), 6.20 (dd, $J_{4'',3''}$ = 5.6 Hz, $J_{4'',2''}$ = 2.2 Hz 1H, H-4''), 5.74 (dt, $J_{8,7}$ = 12.1 Hz, $J_{8,7}$ = 4.5 Hz, 1H, H-8), 5.01 (bdd, $J_{2'',2'}$ = 6.2 Hz, $J_{2'',3''}$ = 1.6 Hz 1H, H-2''), 4.47 (m, 1H, H-9a), 4.10 (m, 2H, H_5, H-2'''), 3.24 (s, 4H, 2H-4''', 2H-5'''), 2.92 (m, 1H, H-5), 2.36 (m, 6H, 2H-2, H-7, 2H-2', H-1'), 1.98 (m, 4H, H-6, 2H-1, H-7), 1.65 (m, 1H, H-6); ^{13}C NMR (62.5 MHz, $CDCl_3$, major isomer) δ 174.3/172.2 (C-3/C-5''), 154.4 (C-3''), 138.3 (C-9), 128.6 (C-8), 123.2 (C-4''), 85.0 (C-2''), 65.3 (C-2'''), 50.7 (C-9a), 47.2 (C-1'), 41.5 (C-1), 38.9/38.8/38.7 (C-5/C-4'''/C-5'''), 30.9 (C-2), 27.5 (C-2'), 24.1 (C-6), 22.1 (C-7); HRMS (ESI+) calcd for $[C_{18}H_{23}NO_3S_2Na^+]$: 388.1012, found: 388.1006.

4.74. *9-[1-(5-Oxotetrahydrofuran-2-yl)propyl]-5,6,7,9a-tetrahydro-1H-pyrrolo[1,2-a]azepin-3(2H)-one, (**75**)*

A commercial suspension of Raney nickel in anhydrous EtOH (activated catalyst 50% slurry in water, 3.9 mL), was thoroughly washed with anhydrous EtOH and then a solution of dithiane **74**

(14 mg, 38 μmol) in dry CH_2Cl_2 (700 μL) was added. The mixture was heated at 40 °C while stirring for 90 min. When TLC analysis (EtOAc/MeOH, 10:1) showed total consumption of **74**, the mixture was warmed to room temperature and then filtered through a short pad of Celite® and concentrated under vacuum. The crude product was purified by column chromatography (EtOAc) to yield a 5:2 diastereoisomeric mixture of **75** as a yellowish syrup (7 mg, 25 μmol, 66%): R_f 0.34 (EtOAc/MeOH, 9:1); IR (ATR) 3404, 2933, 2873, 2363, 1769, 1663, 1462, 1423, 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (dd, $J_{8,7}$ = 8.9 Hz, $J_{8,7}$ = 5.9 Hz) and 5.60 (dd, $J_{8,7}$ = 8.9 Hz, $J_{8,7}$ = 6.0 Hz) (1H, H-8), 4.47 (m, 1H, H-2''), 4.10 (m, 2H, H-5, H-9a), 3.01 (dt, J_{gem} = 13.6 Hz, $J_{5,6}$ = 8.8 Hz, 1H, H-5), 2.89 (m, 1H, H-1'), 2.56 (td, J_{gem} = 10.2 Hz, $J_{2,1}$ = 6.5 Hz, 2H, 2H-2), 2.47 - 1.80 (m, 12H, 2H-1, 2H-6, 2H-7, 2H-3'', 2H-4'', 2H-2'), 0.94 (m, 3H, 3H-3'); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer) δ 176.6/174.5 (C-3/C5''), 140.4/126.3 (C-8/C-9), 82.7 (C-2''), 65.0 (C-9a), 51.6 (C-1'), 38.9 (C-5), 30.9/29.2/27.5/27.0/24.3/24.1/21.9 (C-1/C-2/C-6/C-7/C-3''/C-4''/C-2'), 11.7 (C-3'); HRMS (ESI+) calcd for $[C_{16}H_{23}NO_3Na^+]$: 300.1570, found: 300.1574.

4.75. *9-[1-(5-Oxotetrahydrofuran-2-yl)propyl]hexahydro-1H-pyrrolo[1,2-a]azepin-3(2H)-one (**76**)*

PtO_2 (10 mg, 44 μmol) was added to a solution of **75** (10 mg, 36 μmol) in MeOH (600 μL) and the suspension was stirred under 2.5 atm of H_2 in a Parr vessel for 36 h. Then, the catalyst was filtered through a Celite® pad and the solution concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc) to furnish a diastereoisomeric mixture of **76** as a yellowish syrup (10 mg, 36 μmol, quantitative): R_f 0.30 (EtOAc/MeOH, 9:1); IR (ATR) 3366, 2926, 2855, 1770, 1658, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of isomers) δ 4.65 (m) and 4.48 (m) (1H, H-2''), 4.05 (bd, J_{gem} = 13.8 Hz) and 3.85 (m) (1H, H-5), 3.91 (dt, $J_{9a,9}$ = 17.9 Hz, $J_{9a,1}$ = 5.3 Hz) and 3.52 (ddd, $J_{9a,1}$ = 13.1 Hz, $J_{9a,9}$ = 11.1 Hz, $J_{9a,1}$ = 6.5 Hz) (1H, H-9a), 3.04 (m) and 2.66 (td, J_{gem} = 12.6 Hz, $J_{5,6}$ = 4.9 Hz) (1H, H-5), 2.59 (m, 2H, 2H-4''), 2.32 (m, 4H, 2H-2, H-9, H-3''), 2.13 -1.15 (m, 12H, 2H-1, 2H-6, 2H-7, 2H-8, 2H-2', H-1', H-3''), 1.03 (m, 3H, 3H-3'); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer) δ 176.5/174.3 (C-3(C-5''), 82.1 (C-2''), 60.4 (C-9a), 47.2 (C-1'), 42.9 (C-9), 40.4 (C-5), 31.0/29.7/29.2/29.1/27.4/25.5/22.5 (C-1/C-2/C-6/C-7/C-8/C3''/C4''), 21.0 (C-2'), 13.8 (C-3'); HRMS (ESI+) calcd for $[C_{16}H_{25}NO_3Na^+]$: 302.1727, found: 302.1734.

4.76. *9-[1-(4-Methyl-5-oxo-2,5-dihydrofuran-2-yl)propyl]octahydro-3H-pyrrolo[1,2-a]azepin-3-one (**78**) and 9-[1-(4-Methylene-5-oxotetrahydrofuran-2-yl)propyl]octahydro-3H-pyrrolo[1,2-a]azepin-3-one (**79**)*

LiHMDS (1M in THF, 36 μL, 36 μmol) was added dropwise to a solution of **76** (10 mg, 36 μmol) in anhydrous THF (200 μL) at –78 °C and the mixture was stirred at this temperature for 1 h. After this time, a solution of PhSeBr (9.3 mg, 39 μmol) in anhydrous THF (90 μL) was added at –78 °C and the mixture was stirred at this temperature for 30 min. When TLC analysis (EtOAc) showed total consumption of **76**, the reaction was quenched with saturated aqueous NH_4Cl (0.5 mL) and the mixture was warmed to room temperature. The aqueous layer was extracted with Et_2O (3x1 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography (EtOAc) to yield a complex diastereoisomeric mixture of compounds (11.3 mg), which was solved in anhydrous THF (400 μL) and cooled to –78 °C. LiHMDS (1M in THF 26 μL, 26 μmol) was added dropwise to this solution and the mixture stirred at –78 °C for 1 h. Then, MeI (2 μL, 30 μmol) was added and the mixture was warmed to 0 °C and stirred overnight at this temperature. When the TLC analysis (EtOAc) showed total consumption of the starting material, the mixture was treated with saturated aqueous NH_4Cl (100 μL) and the aqueous phase extracted with Et_2O (3x200 μL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography (EtOAc) to furnish a diastereoisomeric mixture of **77** as a yellowish syrup (3 mg, 7 μmol, 19% yield for the two steps): R_f 0.34 (EtOAc); ^1H NMR (250 MHz, $CDCl_3$, significant signals) δ 7.80 - 7.30 (Ph), 4.58 - 3.58 (H-2'', H-5, H-9a), 2.58 (H-5), 1.69 (br s, CH_3), 1.06 - 0.79 3H-3'). H_2O_2 (30% in wt, 4 μL, 36 μmol) was then added to a solution of **77** (3.0 mg, 7 μmol) in anhydrous CH_2Cl_2 (70 μL) at –10 °C and the mixture was stirred at this temperature for 40 min. After this time, H_2O (50 μL) was added and the mixture was warmed to room temperature. The aqueous phase was extracted with CH_2Cl_2 (2x50 μL) and the combined organic extracts were dried and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc) to furnish a mixture of **78** and **79** as a yellowish syrup (1.1 mg, 3.8 μmol, 56%): R_f 0.16 (EtOAc); HRMS (ESI+) calcd for $[C_{17}H_{25}NO_3Na^+]$: 314.1727, found: 314.1731; **78**: ^1H NMR (400 MHz, $CDCl_3$, significant signals) δ 7.15 - 7.13 (H-3''), 5.07 - 5.03 (H-2''), 4.10 - 4.01 (H-9a), 3.89 - 3.82 (H-5), 2.68 - 2.60 (H-5), 2.07 (s, CH_3), 1.03 - 0.96 (3H-3'). **79**: ^1H NMR (400 MHz, $CDCl_3$, significant signals) δ 6.22 - 6.19 and 5.22 - 5.18 (terminal CH_2).

4.77. *Methyl (E)-3-((1S,9aS)-1-{[tert-butyl(diphenyl)silyl]oxy}-3-oxo-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-9-yl)acrylate (**80**)*

A solution of sodium hydride (17 mg, 425 μmol) and methyl 2-(dimethoxyphosphoryl)acetate (60 μL, 371 μmol) in dry THF (4 mL) was added to a solution of aldehyde **60f** (123 mg, 284 μmol) in dry THF (2 mL) at 0 °C under nitrogen atmosphere. The mixture was allowed to warm to room temperature and stirred overnight. Then, the reaction was quenched with saturated aqueous NH_4Cl (7 mL) and extracted with Et_2O (7 mL). The layers were separated and the aqueous one was extracted with CH_2Cl_2 (3x7 mL). The organic fractions were combined and washed with 5% aqueous NaOH (3x10 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by column chromatography (hexanes/EtOAc, 4:1, to EtOAc) affording ester **80** as a yellow solid (115 mg, 235 μmol, 83%): Mp 151-155 ºC; $[\alpha]_D$ +116.3 (*c* 1.05, $CHCl_3$); IR (ATR) 2925, 2854, 1696, 1625, 1429, 1220, 1269, 1179, 1082, 940 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 6.2 Hz, 2H, 2H-Ar), 7.50 (d, *J* = 6.5 Hz, 2H, 2H-Ar), 7.43 - 7.28 (m, 6H, 6H-Ar), 7.25 (d, $J_{3,2}$ = 16.1 Hz, 1H, H-3), 6.58 (dd, $J_{8',7'}$ = 8.9 Hz, $J_{8',7'}$ = 6.5 Hz, 1H, H-8'), 5.56 (d, $J_{2,3}$ = 16.1 Hz, 1H, H-2), 4.50 (t, $J_{1',2'} = J_{1',9a'}$ = 4.2 Hz, 1H, H-1'), 4.45 (d, $J_{9a',1'}$ = 4.2 Hz, 1H, H-9a'), 4.08 (dd, J_{gem}= 14.0 Hz, $J_{5',6'}$ = 8.3 Hz, 1H, H-5'), 3.77 (s, 3H, CH_3O), 2.98 (tt, J_{gem}= $J_{7',6'}$ = 13.4 Hz, $J_{7',8'} = J_{7',6'}$ = 6.5 Hz, 1H, H-7'), 2.83 (ddd, J_{gem} = 14.0 Hz, $J_{5',6'}$ = 10.8 Hz, $J_{5',6'}$ = 7.6 Hz, 1H, H-5'), 2.33 (dd, J_{gem} = 17.1 Hz, $J_{2',1'}$ = 4.2 Hz, 1H, H-2'), 2.26 (d, J_{gem} = 17.1 Hz, 1H, H-2'), 2.22 - 2.10 (m, 2H, H-7', H-6'), 1.69 (tt, *J* = 13.3 Hz, *J* = 6.5 Hz, 1H, H-6'), 0.97 (s, 9H, Me_3C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4 (C-1), 167.1 (C-3'), 146.3 (C-3), 143.8 (C-8'), 136.1 (C-Ar), 135.9 (C-Ar), 133.4 (C-9'), 133.2 (C-Ar), 132.0 (C-Ar), 129.9 (C-Ar), 127.7 (C-Ar), 127.5 (C-Ar), 115.0 (C-2), 69.1 (C-1'), 67.0 (C-9a'), 51.5 (CH_3O), 41.1 (C-2'), 37.9 (C-5'), 26.7 (Me_3C), 23.6/23.0 (C-6/C-7), 19.0 (Me_3C); HRMS (ESI+) calcd for $[C_{29}H_{35}NO_4SiNa^+]$: 512.2228, found: 512.2227.

4.78. *(1S,9aS)-1-{[tert-Butyl(diphenyl)silyl]oxy}-9-[(E)-3-hydroxyprop-1-en-1-yl]-1,2,5,6,7,9a-hexahydro-3H-pyrrolo[1,2-a]azepin-3-one (**81**)*

In a schlenk vessel, ester **80** (115 mg, 778 μmol) was solved in dry CH_2Cl_2 (2.3 mL) and the resulting solution was cooled down to −78 °C under nitrogen atmosphere. A solution of DIBAL-H (1M in CH_2Cl_2, 940 μL, 940 μmol) was added dropwise and the mixture was stirred 1.5 h at this temperature. Then, the reaction was quenched with a saturated aqueous solution of Rochelle's salt (2 mL) and the mixture was allowed to warm to room temperature and stirred for 15 min. The layers were separated and the aqueous one was extracted with CH_2Cl_2 (4x3 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography (hexanes/EtOAc, 2:1, to EtOAc) to yield alcohol **81** as a yellow oil (92 mg, 200 μmol, 85%): $[\alpha]_D$ +89.9 (*c* 1.65, $CHCl_3$); IR (ATR) 3371, 2930, 2857, 1672, 1427, 1110, 940 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 - 7.52 (m, 4H, 4H-Ar), 7.46 - 7.30 (m, 6H, 6H-Ar), 6.19 (d, $J_{1',2'}$ = 16.2 Hz, 1H, H-1'), 6.11 (dd, $J_{8,7}$ = 9.0 Hz, $J_{8,7}$ = 6.3 Hz, 1H, H-8), 5.51 (dt, $J_{2',1'}$ = 16.2 Hz, $J_{2',3'}$ = 5.8 Hz, 1H, H-2'), 4.50 (t, $J_{1,2} = J_{1,9a}$ = 4.3 Hz, 1H, H-1), 4.49 (d, $J_{9a,1}$ = 4.3 Hz, 1H, H-9a), 4.11 (d, $J_{3',2'}$ = 5.8 Hz, 2H, 2H-3'), 4.06. (dd, J_{gem} = 14.0 Hz, $J_{5,6}$ = 8.3 Hz, 1H, H-5), 2.99 - 2.79 (m, 2H, H-7, H-5), 2.30 (dd, J_{gem} = 17.0 Hz, $J_{2,1}$ = 4.3 Hz, 1H, H-2), 2.23 (d, $J_{2,2}$ = 17.0 Hz, 1H, H-2), 2.17 - 2.00 (m, 2H, H-6, H-7), 1.65 (m, 1H, H-6), 0.99 (s, 9H, Me_3C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5 (C-3), 136.2 (C-Ar), 135.9 (C-Ar), 134.7 (C-8), 133.4 (C-Ar), 133.4 (C-1'), 132.5 (C-9), 129.8 (C-Ar), 127.7 (C-Ar), 127.4 (C-Ar), 125.3 (C-2'), 69.3 (C-1), 67.5 (C-9a), 63.6 (C-3'), 41.3 (C-2), 38.1 (C-5), 26.7 (*Me*$_3$C), 24.0 (C-6), 22.4 (C-7), 19.0 (Me$_3$*C*); HRMS (ESI+) calcd for $[C_{28}H_{35}NO_3SiH^+]$: 462.2459, found: 462.2448.

4.79. *(E)-3-((1S,9aS)-1-{[tert-Butyl(diphenyl)silyl]oxy}-3-oxo-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-9-yl)acrylaldehyde (**82**)*

DMPI (102 mg, 239 μmol) was added slowly to a solution of alcohol **81** (92 mg, 199 μmol) in dry CH_2Cl_2 (2 mL) at room temperature under nitrogen atmosphere and the mixture was stirred for 1 h at the same temperature. Then, the reaction was quenched with 1 mL of a solution prepared by the addition of $Na_2S_2O_3$ (17 g) to a saturated aqueous solution of $NaHCO_3$ (90 ml) and the mixture was stirred for 15 min. The aqueous phase was extracted with CH_2Cl_2 (2x4 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. Column chromatography (hexanes/EtOAc, 2:1, to EtOAc) of the residue provided aldehyde **82** as a yellow solid (81 mg, 177 μmol, 89%): Mp 84-87 °C; $[\alpha]_D$ +75.9 (*c* 0.70, $CHCl_3$); IR (ATR) 2931, 2858, 1678, 1427, 1361, 1110, 938 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (d, $J_{1,2}$ = 7.5 Hz, 1H, H-1), 7.66 - 7.56 (m, 2H, 2H-Ar), 7.55 - 7.49 (m, 2H, 2H-Ar), 7.48 - 7.30 (m, 6H, 6H-Ar), 6.94 (d, $J_{3,2}$ = 16.0 Hz, 1H, H-3), 6.11 (dd, $J_{8',7'}$ = 9.0 Hz, $J_{8',7'}$ = 6.4 Hz, 1H, H-8'), 5.84 (dd, $J_{2,1}$ = 16.0 Hz, $J_{2,3}$ = 7.5 Hz, 1H, H-2), 4.57 (bt, $J_{1',2'} \sim J_{1',9'a} \sim$ 4.1 Hz, 1H, H-1'), 4.48 (bd, $J_{9a',1'}$ = 4.1 Hz, 1H, H-9a'), 4.12 (dd, J_{gem} = 14.0 Hz, $J_{5',6'}$ = 8.5 Hz, 1H, H-5'), 3.03 (tt, *J* = 14.0 Hz, *J* = 7.1 Hz, 1H, H-7'), 2.86 (ddd, *J* = 14.0 Hz, *J* = 10.8 Hz, *J* = 7.6 Hz, 1H, H-5), 2.41 (dd, J_{gem} = 17.1 Hz, $J_{2',1'}$ = 4.1 Hz, 1H, H-2'), 2.36 (d, J_{gem} = 17.1 Hz, 1H, H-2'), 2.31 - 2.14 (m, 2H, H-7', H-6'), 1.73 (tt, *J* = 12.7 Hz, *J* = 5.9 Hz, 1H, H-6'), 0.99 (s, 9H, Me_3C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3 (C-1), 172.4 (C-3'), 153.7 (C-3), 145.9 (C-8'), 136.0 (C-Ar), 135.8 (C-Ar), 134.0 (C-9'), 133.0 (C-Ar), 131.9 (C-Ar), 130.1 (C-Ar), 130.0 (C-Ar), 127.8 (C-Ar), 127.7 (C-Ar), 126.0 (C-2), 69.1 (C-1'), 67.0 (C-9a'), 41.2 (C-2'), 37.9 (C-5'), 26.8 (*Me*$_3$C), 23.5/23.3 (C-6/C-7), 19.0 (Me$_3$*C*); HRMS (ESI+) calcd for $[C_{28}H_{33}NO_3SiNa_2^+]$: 505.2014, found: 505.2017.

4.80. *3-((1S,9aS)-1-{[tert-Butyl(diphenyl)silyl]oxy}-3-oxo-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-9-yl)-3-(5-oxo-2,5-dihydro-2-furan-2-yl)propanal (**83**)*

Aldehyde **82** (20 mg, 103 μmol) was added to a solution of pyrrolidine (5 mg, 20 μmol) and DNBA (4 mg, 21 μmol) in CH_2Cl_2 (0.6 mL) at –20 °C. Then, H_2O (4 μL, 200 μmol) was added and the mixture was stirred for 5 min before the addition of furane **39** (25 μL, 151 μmol). The resulting mixture was stirred overnight at –20 °C and then it was warmed to –10 °C and stirred at this temperature for 48 h. After this time, the mixture was quenched with silica gel, filtered, and the silica washed with CH_2Cl_2 (5 mL). The crude product was purified by column chromatography (EtOAc/MeOH, 10:1) to furnish aldehyde **83** as a yellowish syrup (5 mg, 10 μmol, 10%): ^1H NMR (250 MHz, $CDCl_3$) δ 9.51 (s, 1H; H-1), 7.67 - 7.57 (m, 4H, 4H-Ar), 7.49 - 7.36 (m, 7H, 6H-Ar, H-3''), 6.17 (dd, $J_{4'',3''}$ = 5.8 Hz, $J_{4'',2''}$ = 2.1 Hz, 1H, H-4''), 5.88 (dd, $J_{8',7'}$ = 9.0 Hz, $J_{8,7}$ = 6.3 Hz, 1H, H-8'), 5.05 (dd, *J* = 3.5 Hz, *J* = 1.8 Hz, 1H, H-2''), 4.37 (bt, $J_{1',2'} = J_{1',9a'}$ = 3.9 Hz, 1H, H-1'), 4.20 (bd, $J_{9a',1'}$ = 3.9 Hz, 1H, H-9a'), 4.14 - 3.99 (m, 1H, H-5'), 3.23 - 1.91 (m, 10H, 2H-$_{7'}$, 2H-$_{2'}$, H-$_{5'}$, 2H-6', 2H-2, H-3), 1.05 (s, 9H, Me_3C).

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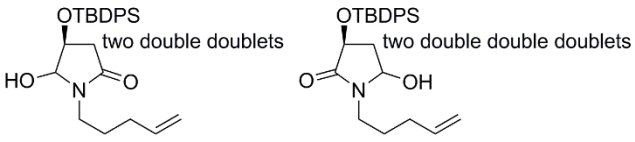
31. The two regioisomers are easily distinguished by the coupling pattern of the ring methylene signals in their ^{1}H NMR spectra.



58f **58f*regio***
(minor regioisomer)

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Supplementary Material

Experimental procedures for the synthetic sequences of Schemes 12 and 18. ^{1}H and ^{13}C NMR spectra of all new compounds and 2D NMR spectra for compounds **9**, **15**, **17**, **22**, **23**, **26** and **30**. X-ray structure determination of compound **9**.