Synthesis of azabicycles *via* cascade aza-Prins reactions: accessing the indolizidine and quinolizidine cores

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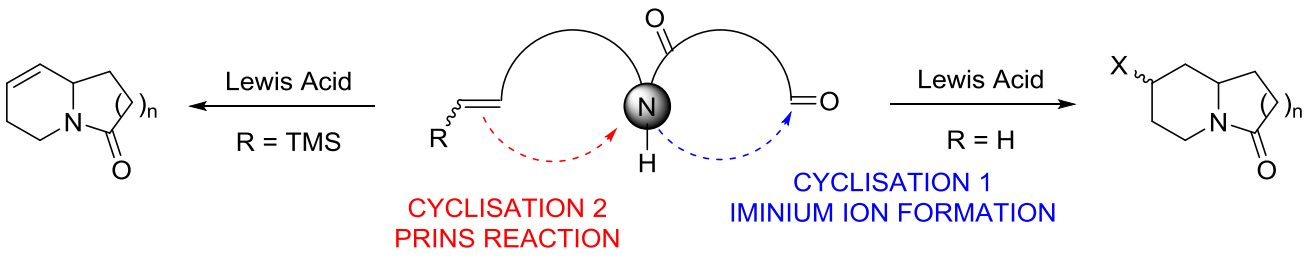
ABSTRACT

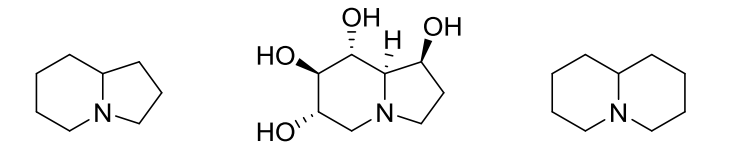


The first detailed study of intramolecular aza-Prins and aza-silyl-Prins reactions, starting from acyclic materials, are reported. The methods allow rapid and flexible access towards an array of [6,5] and [6,6] aza-bicycles, which form the core skeletons of various alkaloids. Based upon our findings on the aza-Prins and aza-silyl-Prins cyclisations, herein we present simple protocols for the intramolecular preparation of the azabicyclic cores of the indolizidines and quinolizidines using a one pot cascade process of *N*-acyliminium ion formation followed by aza-Prins cyclisation and either elimination or carbocation trapping. It is possible to introduce a range of different substituents into the heterocycles through a judicial choice of Lewis acid and solvent(s), with halo-, phenyl- and amido- substituted azabicyclic products all being accessed through these highly diastereoselective processes.

INTRODUCTION

Azabicyclic compounds are ubiquitous in nature, with the quinolizidine and indolizidine alkaloids being prime examples, and which possess a wide range of biological activities. The polyhydroxylated indolizidine alkaloids, such as (+)-castanospermine, have attracted particular attention as glycosidase inhibitors, as well as demonstrating anti-viral (in particular anti-HIV), antitumour and immunomodulation activities. These properties continue to drive the search for novel synthetic approaches towards their preparation. Herein we report a novel and highly efficient cascade process for the rapid synthesis of azabicycles.

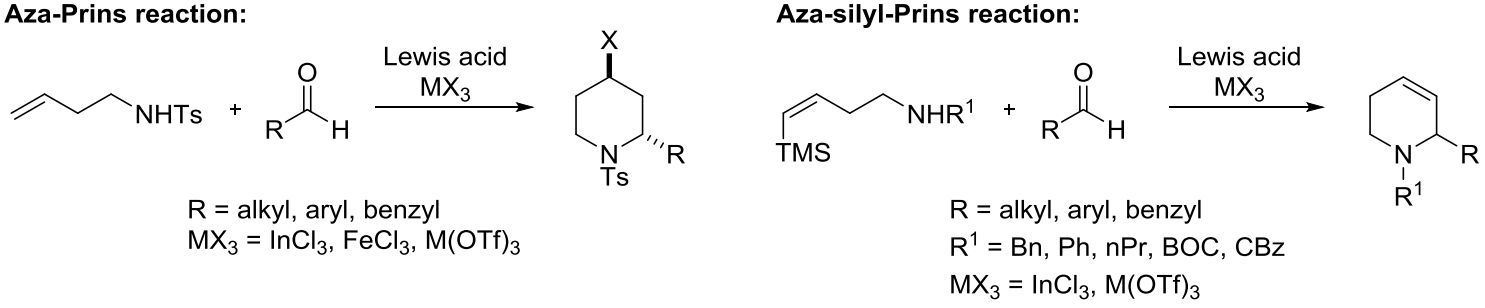
Figure 1. Representative fused azabicycles



Indolizidine core (+)-Castanospermine Quinolizidine core

We have had a long standing interest in the Lewis acid-promoted Prins reaction[1,2] and have, along with others, more recently reported on the nitrogen equivalent of this reaction, the aza-Prins reaction,[3-12] together with its silicon modified counterpart the aza-silyl-Prins reaction.[2,13-16] Both reactions involve the intermolecular reaction of a carbonyl or related compound (aldehyde, ketone or epoxide) with a secondary homoallylic amine in order to form an iminium ion, which then undergoes intramolecular Prins cyclisation to give either piperidines or tetrahydropyridines, depending on the absence or presence of the silicon moiety on the alkene (Scheme 1). The aza-silyl-Prins reaction is highly tolerant of a range of groups on the secondary amine, but is more limited to a sulfonamide in the aza-Prins reaction.

Scheme 1. The aza-Prins[6,17-19] and aza-silyl-Prins[2,13,14] reactions

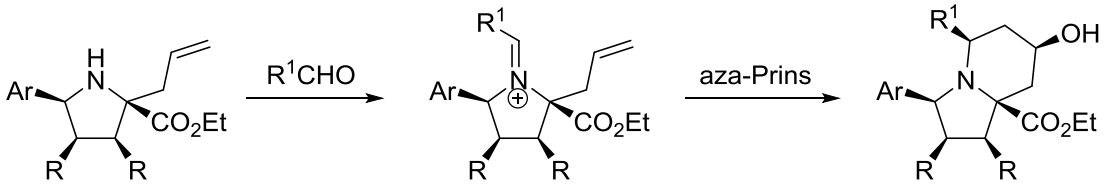


It occurred to us that it may be possible to access the azabicyclic core of various alkaloids by a two-step one-pot cascade process, first involving intramolecular iminium ion formation, followed by Prins cyclisation and either carbocation trapping by a suitable nucleophile or elimination from the resultant carbocation (Scheme 2). Reddy[20], Saikia[21,22], Overman[23] and Waters[24] have all prepared azabicyclic systems using a Prins or related cyclisation process, but have either started from an intact or commercial mono-cyclic system,[24] or have required the sequential formation and purification of the mono-cyclic precursors, followed by a second cyclisation process.[23] Thus the uniqueness and advantage of this approach in the one-pot double cyclisation, forming both rings in a single transformation.

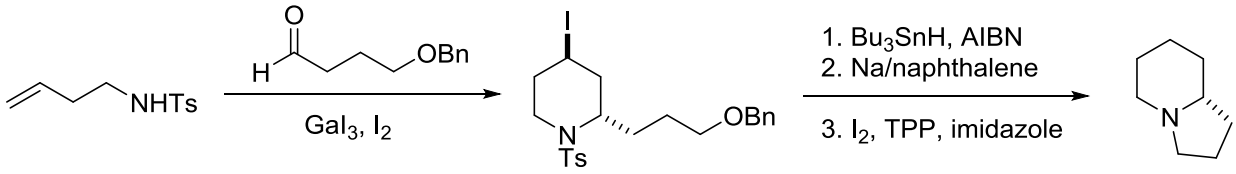
Scheme 2. Previous related work and proposed cascade process

Overman (1989):

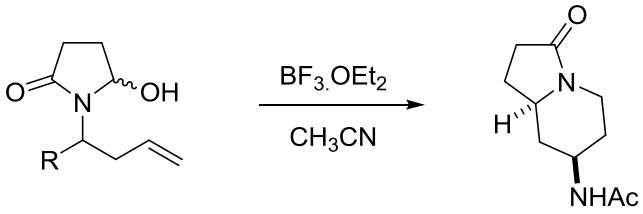
Waters (2012):



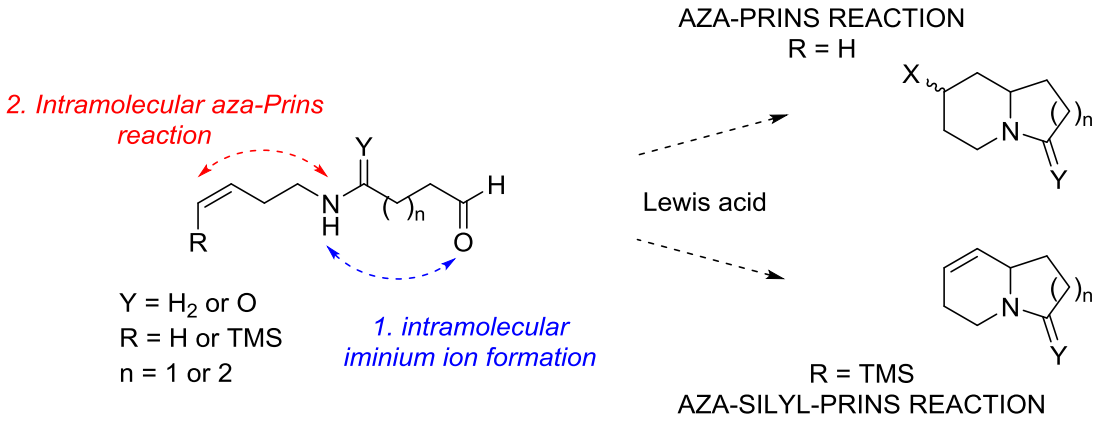
Subba Reddy (2012):



Saikia (2013):



This work:

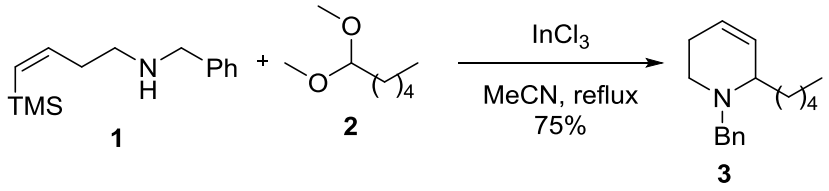


RESULTS AND DISCUSSION

In attempting to make the desired cyclisation precursors, we quickly established that the presence of both an aldehyde and amine in the same precursor was problematic, and that they reacted together before the desired cascade

sequence. Therefore an acetal was considered as a viable alternative. To test the feasibility of using an acetal in an aza-silyl-Prins reaction, 1,1-dimethoxyhexane **2** was reacted with *(Z)-N*-benzyl-4-(trimethylsilyl)but-3-en-1-amine **1** and gave the corresponding tetrahydropyridine **3** in good yield (Scheme 3).

Scheme 3. Aza-silyl-Prins reaction using 1,1-dimethoxyhexane



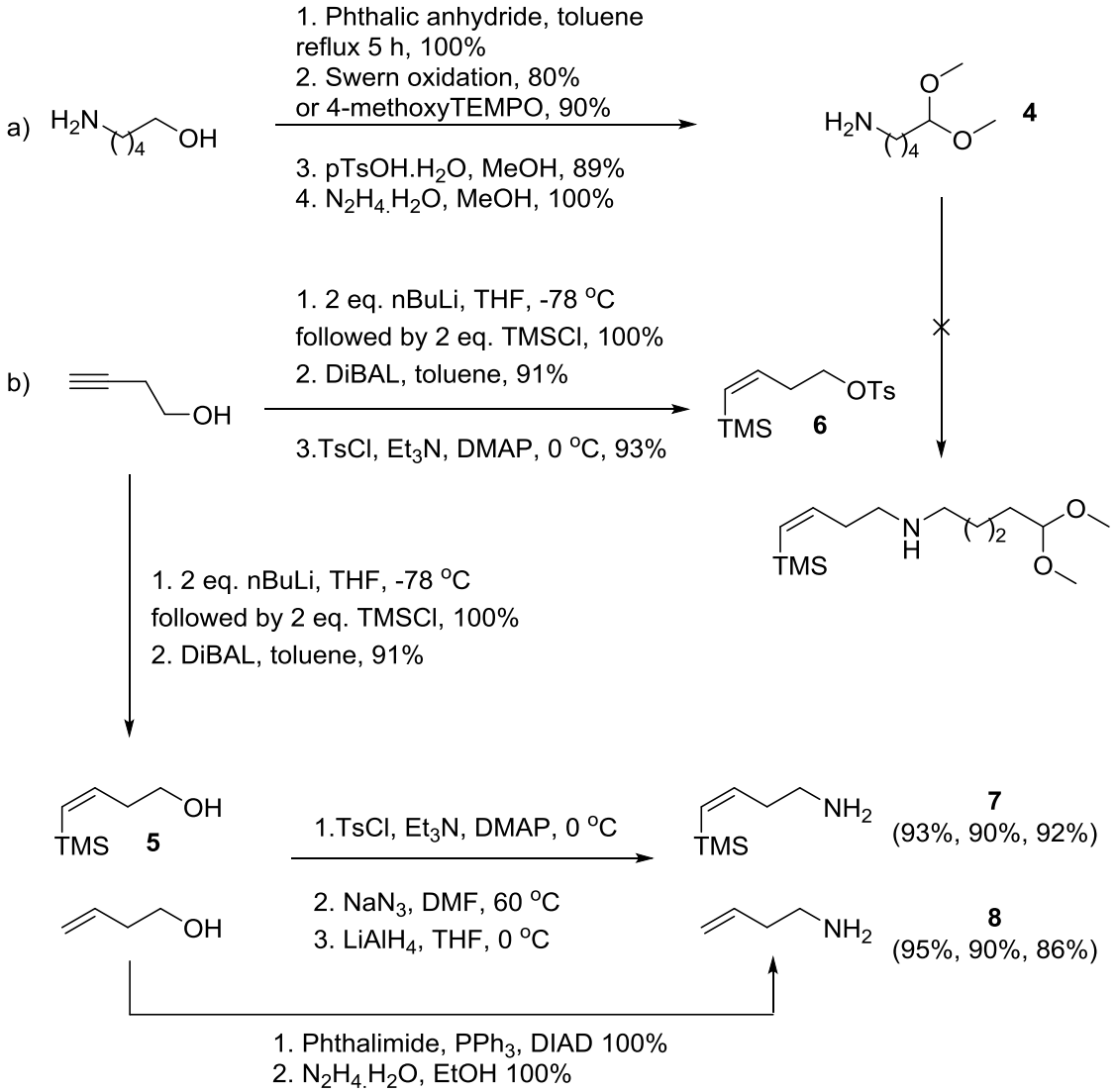
Therefore with the strategy of using an acetal in mind, both the required secondary amine and amide precursors were prepared using related routes. It was envisaged that the cyclisation precursors could be obtained by two possible routes, namely amine displacement of a suitably activated homoallylic alcohol or peptide coupling of a homoallylic amine with a carboxylic acid.

The former method was examined first, with 5,5-dimethoxypentylamine **4** prepared in four steps and in 80% overall yield from 5-aminopentanol (Scheme 4a). (*Z*)-4-(Trimethylsilyl)but-3-en-1-yl 4-toluenesulfonate **6** was obtained from 3-butyn-1-ol *via* (*Z*)-4-(trimethylsilyl)but-3-en-1-ol **5**. Unfortunately, all attempts at coupling these two compounds failed to give the desired cyclisation precursor, with the product of amine dialkylation being the main product obtained.

The latter amide coupling approach was then examined. The two prerequisite amines **7** and **8** were prepared from the corresponding alcohols, namely 3-buten-1-ol and (*Z*)-4-(trimethylsilyl)but-3-en-1-ol **5**, by tosylation, displacement with azide and reduction with lithium aluminium hydride in 70% (5 steps from 3-butyn-1-ol) and 74% (from 3-buten-1-ol) overall yields respectively (Scheme 4b). **8** could also be prepared quantitatively using Mitsunobu chemistry with phthalimide followed by cleavage using hydrazine monohydrate.

4,4-Dimethoxybutanoic acid **9** was prepared in two steps from methyl 4-nitrobutanoate *via* a Nef reaction followed by basic methanolysis, in 86% overall yield (Scheme 4c). 5,5-Dimethoxypenanoic acid **10** was also prepared in two steps by ozonolysis of cyclopentene followed by methanolysis, in 47% overall yield (Scheme 4d).

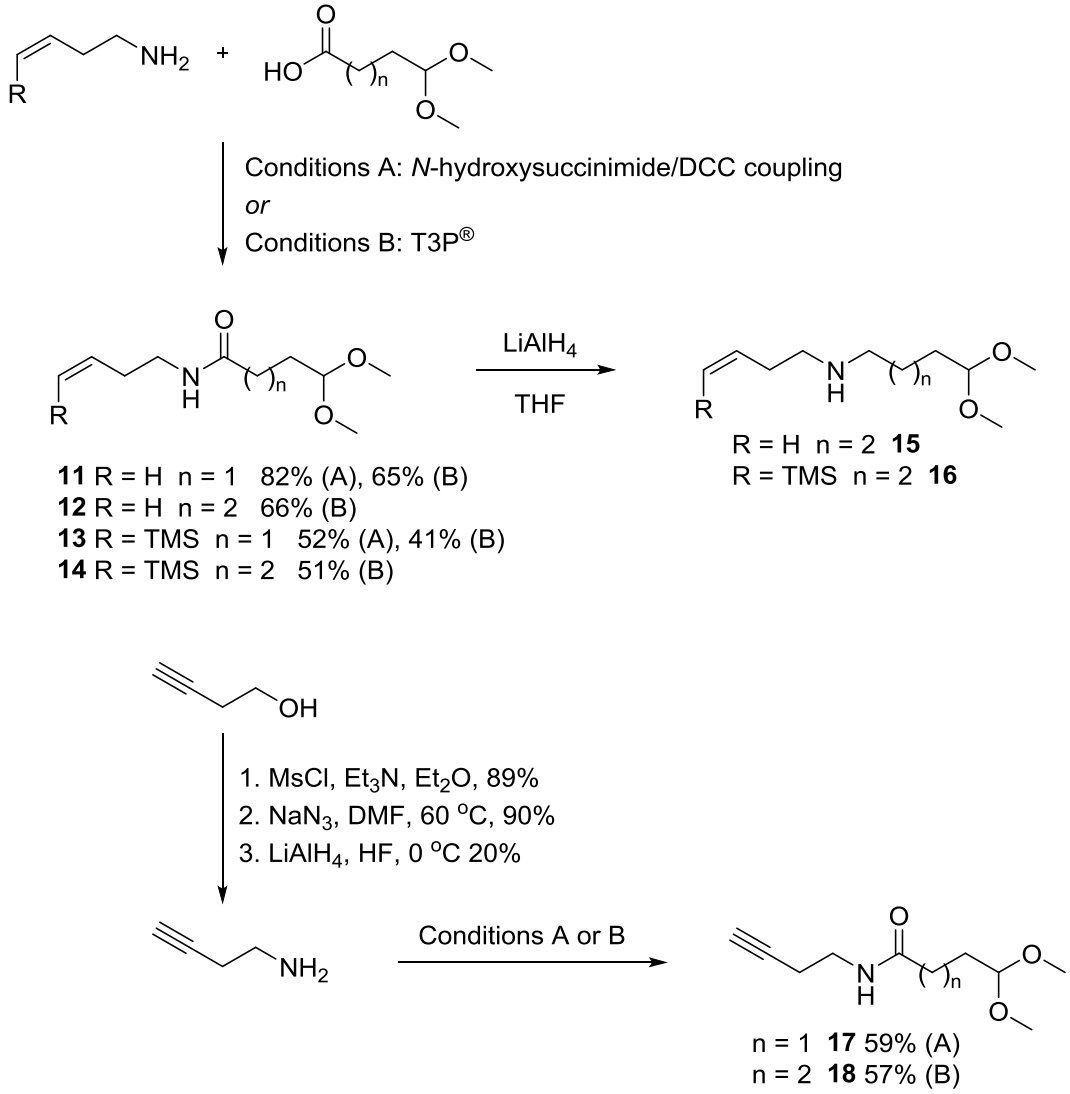
Scheme 4. Synthesis of cyclisation precursors.



Two methods were employed for the amide coupling reactions (Scheme 5). Acids **9** and **10** were activated with *N*-hydroxysuccinimide prior to coupling the active esters with either amine **7** or **8** using *N,N*-dicyclohexylcarbodiimide. Alternatively, the peptide coupling reagent *n*-propane phosphonic acid cyclic anhydride, T3P®,[25] was also successfully employed for the direct coupling of the acids and amides, albeit in slightly lower yields, but with the advantage that purification was achieved by simple aqueous extraction. Finally, the secondary amines **15** and **16** were prepared by

lithium aluminium hydride reduction of the amides **11** and **13**. But-3-ynylamine was prepared from 3-butyn-1-ol by tosylation, azide displacement and $LiAlH_4$ reduction and the T3P® method again used to prepare the alkynyl derivatives **17** and **18**. Thus all the required linear cyclisation precursors could be obtained easily and in high overall yields.

Scheme 5. Synthesis of cyclisation precursors.

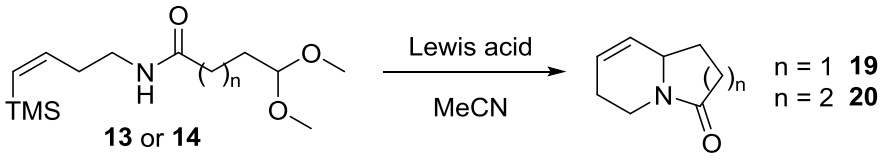


We have previously reported the use of indium trichloride in acetonitrile at reflux as being highly effective for promoting the aza-silyl-Prins reaction with aldehydes[2,3,13,14] and indeed this was successful in promoting an intermolecular aza-silyl-Prins reaction with an acetal (Scheme 3). However, these conditions failed to give any of the desired aza-bicycle when secondary amines **15** or **16** were employed, with starting material recovered. Changing the solvent to toluene, and heating at reflux, gave traces of product but rapid decomposition of the starting material was observed, at a rate considerably faster than the cyclisation. The addition of 4Å molecular sieves did not influence the outcome of the reaction. It is postulated that the Lewis acid may be complexing with the amine rather than activating

the acetal, preventing the first cyclisation occurring. Thus indium trichloride is seen as a promoter of the *inter*molecular aza-Prins reaction with acetals, but a "poison" of an *intra*molecular variant.

The same Lewis acid screening was then applied to the aza-silyl-Prins reaction amide precursors **13** and **14**. Gratifyingly, double cyclisation now took place relatively easily with a number of Lewis acids, with the [6,5] and [6,6] bicycles being obtained in good yield, particularly when employing scandium triflate (Table 1 entries 2 & 5) and indium triflate (Table 1 entries 1 & 4) as Lewis acids.

Table 1. Iminium ion formation/Aza-Prins cyclisation cascades



	n	Lewis Acid[a]	Product	% Yield[b]
1	1	$In(OTf)_3$	19	32
2	**1**	**$Sc(OTf)_3$**	**19**	**75**
3	1	$InCl_3$	19	17
4	**2**	**$In(OTf)_3$**	**20**	**60**
5	**2**	**$Sc(OTf)_3$**	**20**	**64**
6	2	$InCl_3$	20	traces

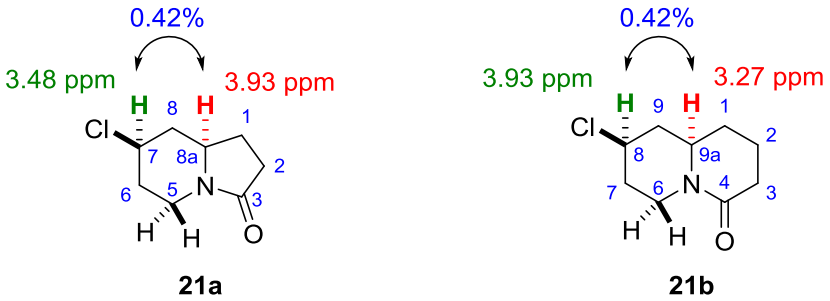
[a]All reactions were performed at reflux temperature; [b]purified, isolated yields.

Given that numerous indolizidine and quinolizidine alkaloids (Figure 1) are poly-hydroxylated, frequently at the positions of the alkene produced in **19** and **20**, attempts were made to perform an Upjohn OsO_4/NMO dihydroxylation reaction on the [6,5] product **19** (Table 1 entry 2). With no starting material or product isolated, the reaction was repeated in d_6-acetone/D_2O (9:1) and monitored by NMR: the complete disappearance of the olefin signals at δ = 5.77 and 5.67 was observed, and two new multiplet signals at δ = 3.71 and 3.85 appeared (for 2 x C**H**(OH)), indicating the formation of two hydroxyl groups. Unfortunately, the diol was found to be very water soluble and could not be extracted and purified after destruction of the osmate ester.[26] Attempts to capture the diol as either the acetate (using acetyl chloride) or 4-nitrobenzoate ester (from 4-nitrobenzoyl chloride) both failed. An identical outcome was observed

when using **20**: when the reaction was followed by ^{1}H NMR, the two alkene peaks at δ = 5.81 and 5.50 rapidly disappeared to be replaced by multiplets at δ = 3.74 and 4.01, but again the product was completely water soluble.

With a successful aza-silyl-Prins route into the indolizidine and quinolizidine cores to hand, attention turned to utilizing the aza-Prins reaction to a similar end. As shown in Table 2, a number of Lewis acids were highly efficient at promoting the double cyclisation: iron trichloride, indium trichloride and indium tribromide were all highly successful promoters and provided a nucleophile for capture. Iron trichloride also gave the best diastereomeric ratios, *ca*. 9:1 (Table 2 entries 1 & 8). The yields of the [6,6] system with any particular Lewis acid were generally higher than the equivalent [6,5] system with the same Lewis acid under identical conditions. Intriguingly, when using Lewis acid triflates and boron trifluoride, a mixture of two inseparable unsaturated products **23a** & **23b** was isolated as the major product, along with small amounts of the fluoride-trapped adduct. In all cases, diastereomeric ratios were measured from the reaction mixture by comparing the integration of the signals for the C(5)H_2 (6,5 adduct) or C(6)H_2 (6,6), which were clearly separate in each diastereoisomer (Figure 2). NOE values consistently identified the major adduct in both the (6,5) and (6,6) systems as the *cis* product.

Figure 2. Diastereomeric ratio determination and NOE measurements for 21a (Table 2 entry 2), clearly showing *d.r.*=4:1 from integration of peaks for H-C(5) at δ = 4.16:4.03 and 3.13:2.66



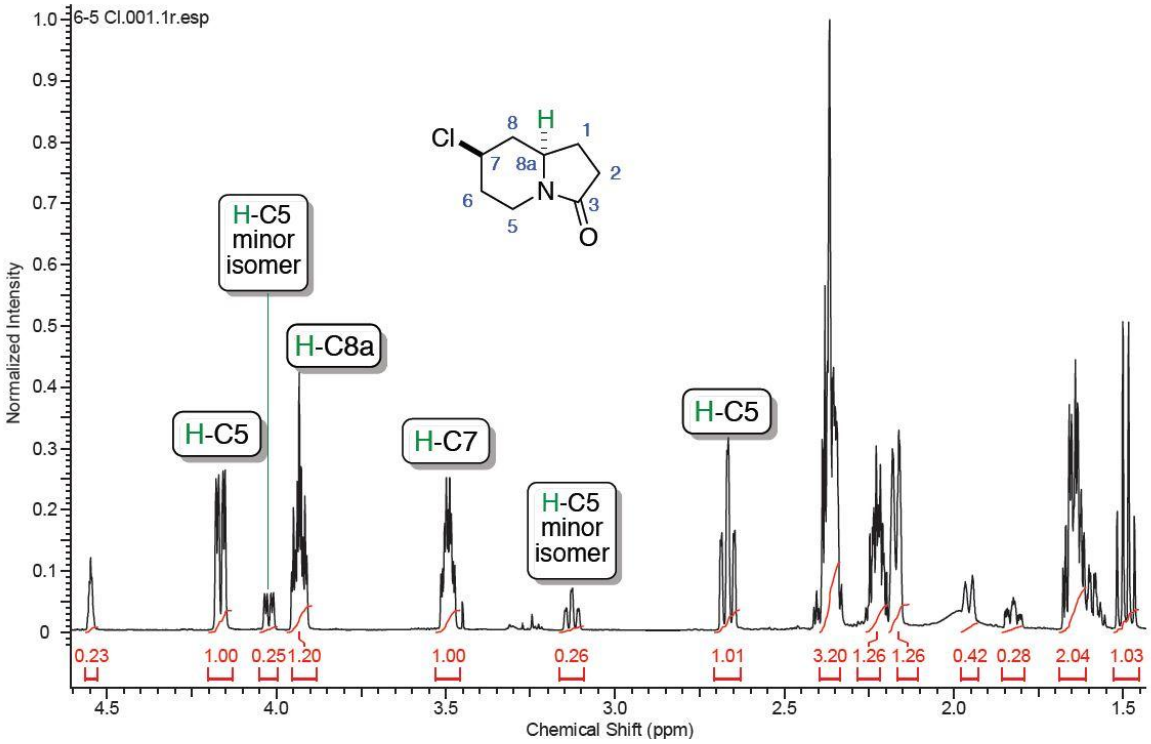
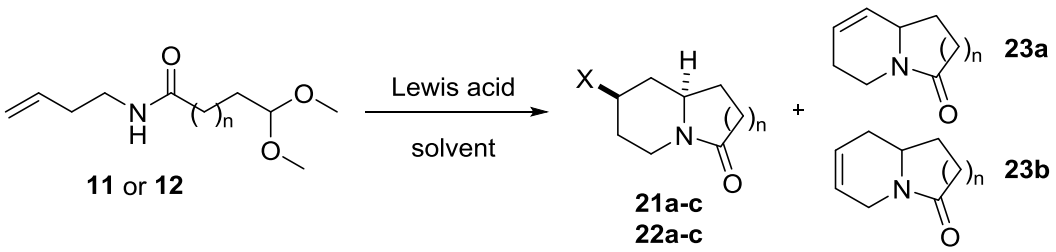


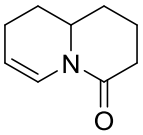
Table 2. Iminium ion formation/Aza-Prins cyclisation cascades



	n	Lewis Acid[a]	Solvent	Product	% Yield[b] (X=)	d.r.[c]	% Yield 23a+b (mixture)[b]
1	1	**$FeCl_3$**	**CH_2Cl_2**	**21a**	**94 (Cl)**	**9:1**	
2	1	$InCl_3$	CH_2Cl_2	21a	45 (Cl)	4:1	
3	1	BBr_3	CH_2Br_2	21b	51 (Br)	4:1	
4	1	$InBr_3$	CH_2Br_2	21b	16 (Br)	4:1	
5	1	$BF_3.OEt_2$	CH_2Cl_2	21c	Traces (F)	1:1	43
6	1	$In(OTf)_3$	CH_2Cl_2	21a	6 (Cl)	-	7
7	1	$In(OTf)_3$	MeCN		0	-	5

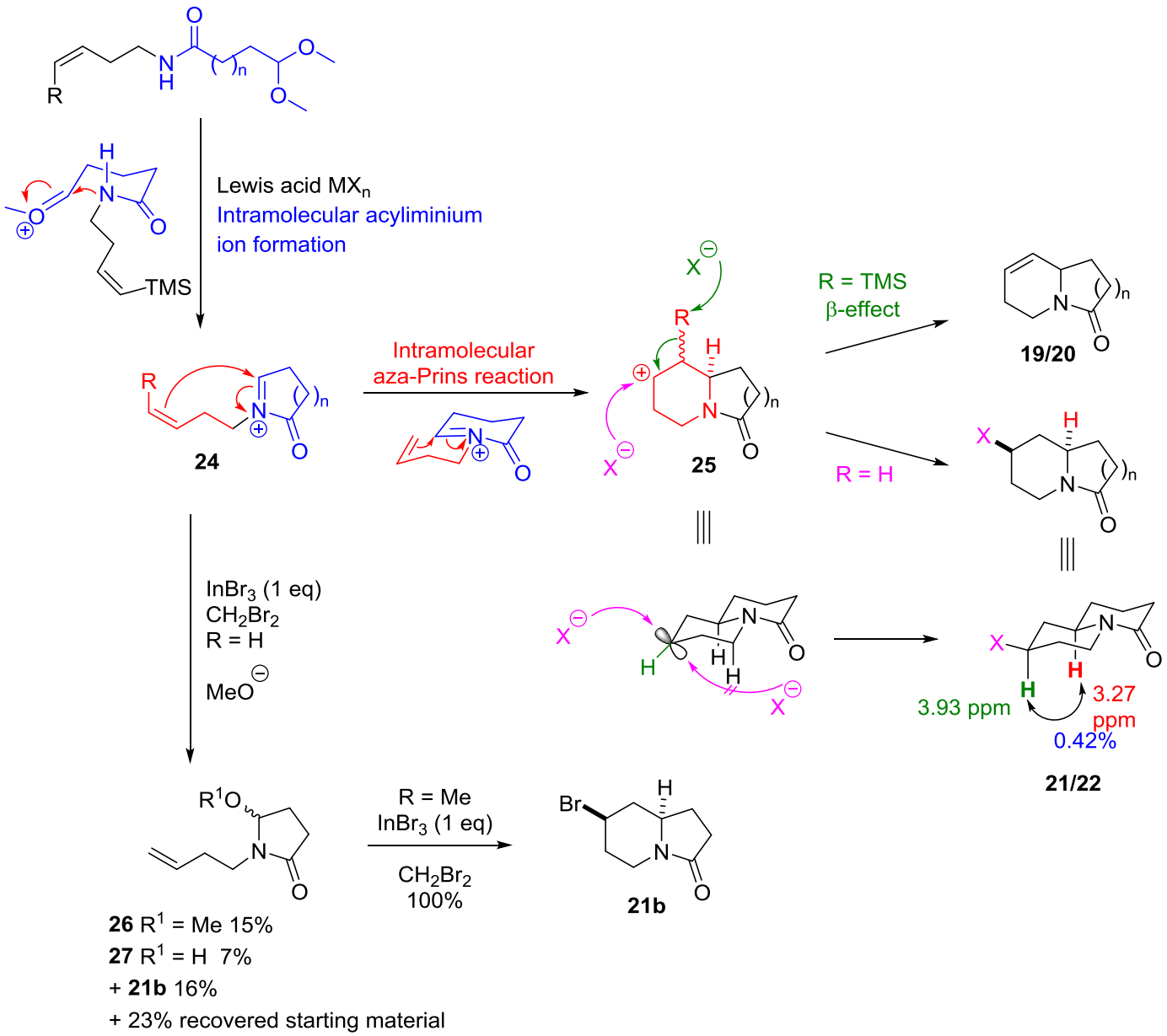
8	2	**$FeCl_3$**	**CH_2Cl_2**	**22a**	**86 (Cl)**	**9:1**	-
9	2	**$InCl_3$**	**CH_2Cl_2**	**22a**	**64(Cl)**	**7:3**	-
10	2	**$InBr_3$**	**CH_2Br_2**	**22b**	**96 (Br)**	**7:3**	-
11	2	$BF_3.OEt_2$	cHex	22c	25 (F)	1:1	32[d]

[a]All reactions were performed with 1 equiv. Lewis acid and at reflux temperature; [b]purified, isolated yields. [c]d.r.'s were determined by NMR integration of the signal for C(5)H_2 or C(6)H_2. [d]An additional third unsaturated product **23c** was also observed just in this particular reaction.



23c

When using 1 equiv. $InBr_3$ (Table 2 entry 4), an intriguing product that is indicative of half-cyclisation, was also isolated. This leads us to postulate on the mechanism of the double cyclisation process (Scheme 6). It is thought that first, intramolecular Lewis acid-promoted acyl iminium ion (**24**) formation takes place. This process is followed by an intramolecular aza-Prins cyclisation, to give the secondary cyclic carbocation (**25**). The ultimate reaction product is then dependent upon the nature of the substituent on the alkene in the starting material. When this was a *Z*-vinylsilane (terminal TMS group), the carbocation is presumably stabilised by the β-effect from silicon, and elimination occurs to give the single alkene product (**19** or **20**), with no regioisomers. However, when the alkene was un-substituted, there is no such stabilisation or favourable elimination reaction that can take place, so an external nucleophile, normally from the Lewis acid, is trapped by the carbocation (**21 or 22**). An exception to this can be found in Table 2 entry 4, where several additional products were observed in addition to the desired product: the intramolecular acyliminium ion is trapped by the methoxide anion giving **26**. It is highly likely that this remained as part of a tight ion pair during the oxonium ion formation/cyclisation to acyliminium ion process, and thus trapping was facile, although this product has not been observed in any other attempted double cyclisation. The addition of 1 equiv. of $InBr_3$ to the methoxy-intermediate provided bicycle **21b** in quantitative yield (Scheme 6). This problem of incomplete cyclisation could therefore be overcome by employing greater than 2 equiv. of Lewis acid in the reaction. Since all reactions in Table 2 were performed with 1 equiv. of Lewis acid, this suggests that some Lewis acids are able to promote the first cyclisation but not the second. The best yields obtained in Table 2 for the 'double cyclisation approach' are far superior to any two-step sequential cyclisation approach to the same targets.

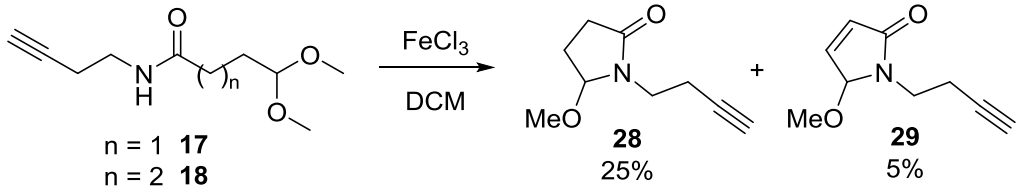


Scheme 6. Proposed mechanism and origin of stereochemical outcome for the aza-silyl-Prins and aza-Prins cyclisations.

Thus overall, the examples presented in Tables 1 and 2 and Scheme 6 may be considered as *N*-acyliminium ion-type cyclisations, given that the double cyclisation did not proceed when Y = 2xH (Scheme 2). Acyliminium ion cyclisations have been comprehensively reviewed[27,28] and these reviews cover many related examples of bicycle formation where one ring is already in place, and the second is formed *via* an acyliminium cyclisation (Scheme 2). However, Hart has reported the only related example of a double cyclisation, employing formic acid as the promotor of a double cyclisation[29] in the total synthesis of the Lythraceae alkaloids Lythrancepine II and III.[30,31]

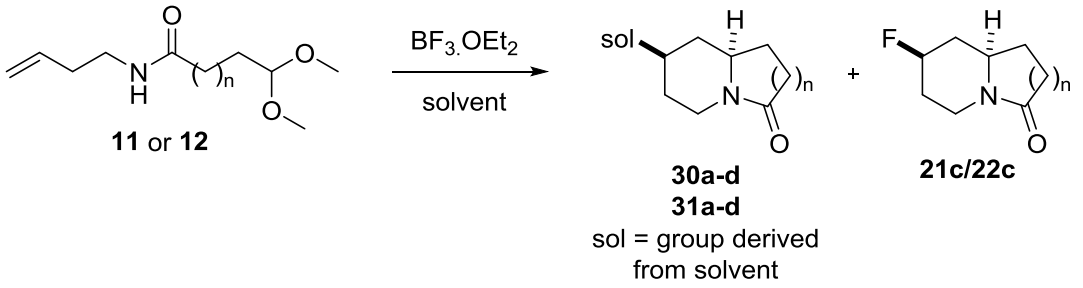
Given Martín's success in the Prins cyclisation of alkynes,[4,32] we investigated the intramolecular cyclisation of precursors **17** and **18**. Neither gave products of double cyclisation. Cyclisation of **17** gave two products, **28** and **29**, derived from the initial cyclisation but no subsequent Prins reaction and **18** gave a complicated mixture from which no compounds could be characterised.

Scheme 7. Attempted alkyne aza-Prins reaction



The incorporation of alternative nucleophiles, in place of the anion from the Lewis acid, during a Prins cyclisation has been reported and is an attractive feature of the reaction.[17,33-35] This also adds a further layer of complexity to the cascade process, making it now three sequential steps: following cyclisation/iminium ion formation and aza-Prins cyclisation, the transformation may be terminated with Friedel-Crafts or Ritter reaction. In general, the trapping of an external nucleophile occurs most readily when employing a Lewis acid poor in providing an anion for capture. With this in mind, the double cyclisation was attempted using boron trifluoride, which had been shown to be poor itself at supplying a nucleophilic anion, with the aim that the solvent may be incorporated favourably and rapidly instead (Table 3).

Table 3. Capturing alternative nucleophiles during the double cyclisation.



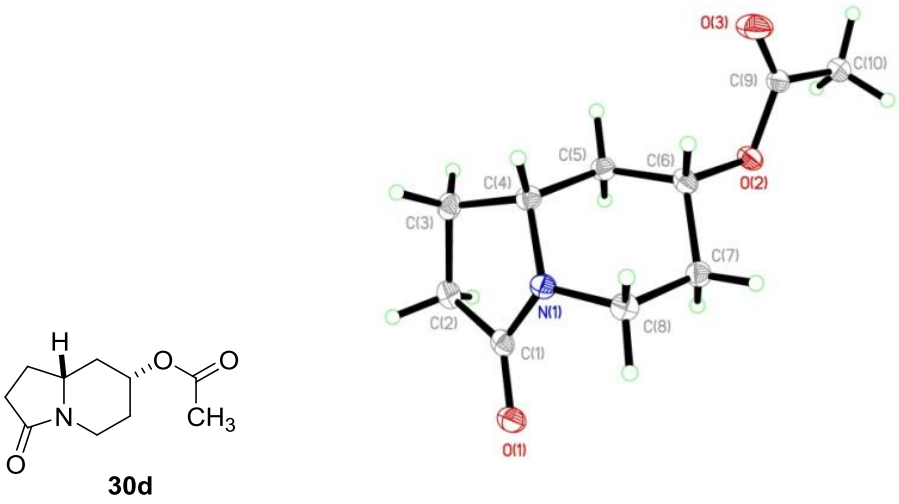
	n	Solvent	sol =	Product	% Yield[a]	Product	% Yield[b]
1	1	PhH	Ph	30a	20	21c	36
2	1	MeCN	NHAc	30b	2 (NHAc)	21c	Traces

				30c	40 (NH_2)		
3	1	EtOAc	OAc	30d	40	21c	4
4	2	PhH	Ph	31a	23	22c	33
5	2	MeCN	NHAc	31b	1	22c	2
6	2	EtOAc	OAc	31c 31d	4 (OAc) 5 (OH)	22c	20

[a]isolated and purified yield of solvent-trapped adduct; [b]isolated and purified yield of F-containing product

Both Prins-Friedel-Crafts (entries 1 & 4) and Prins-Ritter (entries 2 & 5) reactions proceeded in modest yields, in both [6,5] and [6,6] systems. Surprisingly, the *O*-acetyl group, from ethyl acetate, was also found to incorporate in modest yield (entries 3 & 6). Pleasingly, the OAc trapped indolizidine (entry 3) was obtained as a single diastereoisomer in crystalline form (Figure 3), confirming the proposed stereochemistry from the NMR data.

Figure 3. 3-oxooctahydroindolizin-7-yl acetate **30d**. Displacement ellipsoids are drawn at the 50% probability level.



CONCLUSIONS

In conclusion, we have shown that both the aza-Prins and aza-silyl-Prins reactions may be utilised for the preparation of azabicycles, the core structure for accessing indolizidine and quinolizidine alkaloids. The current approach offers a number of advantages over existing methods for accessing the same architectures, namely good yields, starting from

acyclic precursors and the ability to incorporate a range of nucleophiles in the bicyclic products. The Lewis acids $FeCl_3$ (for n=1) and $FeCl_3$, $InCl_3$ and $InBr_3$ (for n=2) were particularly efficient at promoting double cyclisations. The scope and limitations of these reactions with respect to additional substituents and applications, will be reported in due course.

EXPERIMENTAL SECTION

GENERAL DETAILS

Commercially available reagents were used as supplied. All solvents were pre-dried prior to use. All reactions were carried out under anhydrous conditions unless otherwise stated, and all glassware, syringes and needles were oven-dried and then allowed to cool prior to use in experiments. Infrared spectra were recorded in the range 4000-600 cm^{-1}, obtained directly as either solids or neat liquids. Chemical shifts in ^1H NMR spectra are reported in δ (ppm) relative to residual solvent signals $CDCl_3$ δ_H = 7.26 ppm; δ_C = 77.23 ppm or d_6-DMSO δ_H = 2.50; δ_C = 39.51. Multiplicities of signals are reported using standard abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. Coupling constants (*J*) are reported in hertz. Low resolution masses were recorded in EI mode incorporating an SL Ion Trap. High resolution mass spectra were recorded using a LTQ Orbitrap XL with resolution up to 100,000 (FWHM). Fourier Transform mass spectrometry was performed for HRMS measurements.

General Procedure 1: Tosylation of alcohols (on 35 mmol scale)

To a cooled solution of homoallyl alcohol or penten-1-ol (1 equiv.) in CH_2Cl_2 (2 mL per mmol) were added DMAP (0.6 equiv.) and *p*-TsCl (1.2 equiv.) at 0 °C. Et_3N (1 equiv.) was then added dropwise and the solution was stirred at 0 °C until TLC analysis showed complete consumption of the starting alcohol. The solution was diluted with Et_2O (2 mL per mmol) and stirred for another 30 min. Precipitated solid was removed by filtration and the resulting solution washed with 10% aqueous copper sulfate solution (2 x 1.1 mL), followed by 15% aqueous $NaHCO_3$ solution (1.1 mL) and finally brine (0.9 mL per mmol). The organic phase was dried ($MgSO_4$), filtered, and volatile components were removed under reduced pressure and the residue purified by flash column chromatography (PE:Et_2O 1:1) to yield the tosylated alcohol.

General procedure 2: Coupling reaction by T3P® (on 3 mmol scale)

To a stirred solution of 4,4-dimethoxybutanoic acid **6** or 5,5-dimethoxypentanoic acid **7** (1 equiv.) and T3P® (1.15 equiv.) in dry EtOAc (8 mL per mmol) were added sequentially Et_3N (2 equiv.) and (*Z*)-4-(trimethylsilyl)but-3-en-1-amine **4** or 3-buten-1-amine **5** (1 equiv.). After complete consumption of the starting acid was detected by TLC analysis, the mixture was acidified to pH 7 by the addition of 1.0 M aqueous HCl and the product was extracted into EtOAc (10 mL per mmol). The organic layer was washed with water (2 x 10 mL per mmol) followed by brine (10 mL per mmol), dried ($MgSO_4$) and the volatiles removed under reduced pressure to yield the desired amide, which was used without further purification.

General procedure 3: Azidation of tosylated alcohol (on 120 mmol scale)

NaN_3 (3 equiv.) was added portionwise to but-3-en-1-yl toluene-4-sulfonate or (*Z*)-4-(trimethylsilyl)but-3-en-1-yl 4-toluenesulfonate (1 equiv.) in DMF (2 mL per mmol). The resulting solution was heated and stirred to 60 °C for 2 h. After cooling to rt, the mixture was poured into a solution of Et_2O:H_2O (7 mL per mmol, 3:7, v/v). After stirring for 30 min, the aqueous layer was separated, and the organic layer extracted with water (3 x 1 mL per mmol). The aqueous layer was combined with the aqueous extracts and this was extracted with Et_2O (3 x 1.3 mL per mmol) and the combined organic extracts were washed with saturated aqueous LiCl (1.3 mL per mmol) and brine (1.3 mL per mmol). The resulting organic solution was dried ($MgSO_4$), filtered, the solution was concentrated under reduced pressure and the residue subjected to flash column chromatography (PE:Et_2O 9:1) to yield the pure azide.

General procedure 4: Intramolecular aza-silyl-Prins reaction (on 0.70 mmol scale)

To a Lewis acid (1 equiv.) suspension in MeCN (3.5 mL per mmol) heated to reflux was added a solution of (*Z*)-4,4-dimethoxy-*N*-(4-(trimethylsilyl)but-3-en-1-yl)butanamide **10** or (*Z*)-5,5-Dimethoxy-*N*-(4-(trimethylsilyl)but-3-en-1-yl)pentanamide **11** (1 equiv.) in MeCN (1.5 mL per mmol) dropwise over 1 min. The mixture was stirred at reflux for 48 h or until GC-MS analysis showed complete disappearance of the amide peak. The solution was cooled to rt, poured into a biphasic solution of CH_2Cl_2 (4 mL per mmol) and water (8 mL per mmol) and stirred for 30 min. The organic layer was separated, the aqueous layer extracted with CH_2Cl_2 (3 x 2 mL per mmol). Combined organic layers were washed with brine (4 mL per mmol), dried ($MgSO_4$), filtered and volatiles were evaporated under reduced pressure and purification by flash column chromatography yielded the unsaturated *N*-fused bicycle.

General procedure 5: Intramolecular aza-Prins reaction (on 1 mmol scale)

N-(But-3-en-1-yl)-4,4-dimethoxybutanamide **8** or *N*-(but-3-en-1-yl)-5,5-dimethoxypentanamide **9** (1 equiv.) was mixed with the solvent (3.5 mL per mmol) for 5 min and the Lewis acid (1 equiv.) was added. The mixture was stirred for 48 h or until GCMS analysis showed complete disappearance of the amide. Water (5 mL per mmol) was added to quench the reaction and the mixture was stirred for 30 min. The organic layer was separated, and the aqueous layer extracted with solvent (3 x 4 mL per mmol). The combined organic solutions were washed with brine (4 mL), dried (MgSO4), filtered, and volatile components were evaporated under reduced pressure. Purification of the residue by flash column chromatography yielded the bicyclic derivative.

1. Precursor Syntheses

(Z)-4-(Trimethylsilyl)but-3-en-1-ol (5)[2]

To a cooled solution of DiBAL (1.0 M in hexane; 90 mL, 90 mmol, 3 equiv.) in Et_2O (100 mL) at 0 °C was added 4-(trimethylsilyl)but-3-yn-1-ol (4.27 g, 30 mmol, 1 equiv.) in Et_2O (35 mL) dropwise over 15 min. The reaction was heated at reflux overnight. After cooling to 0 °C, the reaction was quenched by the dropwise addition of aqueous H_2SO_4 (2.0 M; 120 mL) over 30 min and stirred for 45 min, warming gradually to rt. The mixture was filtered through celite®, diluted with Et_2O (66 mL), the organic layer separated and the aqueous layer extracted 3 times with Et_2O (40 mL). The combined organic layers were washed with ice cold water (135 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Purification of residues by distillation under reduced pressure (65 °C, 2 mmHg) yielded the *title compound* (3.94 g, 91 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.16 (1H, dt, *J* 14.3, 7.4), 5.55 (1H, dt, *J* 14.3, 1.3), 3.54 (2H, d, *J* 6.5), 2.26 (2H, d, *J* 6.5), 1.50 (1H, bs), 0.00 (9H, s); *m/z* (EI^+) 141 (1% [$C_8H_{17}Si$]), 83 (25% [C_6H_{11}]), 101 (30% [C_4H_9OSi]), 129 (60% [$C_6H_{13}OSi$]), 75 (100% [$(CH_3)_2HSi^+$]).

(*Z*)-4-(Trimethylsilyl)but-3-en-1-yl 4-toluenesulfonate (6)

According to general procedure 1, to a cooled solution of (*Z*)-4-(trimethylsilyl)but-3-en-1-ol **5** (2.29 g, 15.9 mmol) in CH_2Cl_2 (32 mL) were added DMAP (1.17 g, 9.54 mmol), *p*-TsCl (3.63 g, 19 mmol) and Et_3N (2.20 mL, 15.9 mmol) at 0 °C after 5 h TLC analysis showed the complete consumption of starting alcohol. Work up was carried out based on general procedure **1**. Purification of the residue by flash column chromatography (PE:Et_2O 1:1) yielded the *title*

compound (4.41 g, 93%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.79 (2H, d, *J* 7.8), 7.34 (2H, d, *J* 7.8), 6.12 (1H, dt, *J* 14.1, 7.1), 5.64 (1H, dt, *J* 14.1, 1.2), 4.03 (2H, t, *J* 6.9), 2.50-2.45 (2H, m), 2.45 (3H, s), 0.07 (9H, s); *m/z* (EI^+) 165 (10% $[C_4H_9SO_3Si]^+$), 283 (20% $[C_{13}H_{20}O_3SSi]^+$), 91 (35% $[C_7H_7]^+$), 229 (100% $[(C_4H_8)SO_3C_7H_8]$).

_N_-Benzyl-_N_-(_Z_)-(4-trimethylsilylbut-3-enyl)amine (1)[2,36]

Benzylamine (8.04 g, 75.00 mmol, 5 eq.) was warmed to 80 °C under nitrogen before adding a solution of (*Z*)-4-(trimethylsilyl)but-3-en-1-yl 4-toluenesulfonate **6** (4.48 g, 15.00 mmol, 1 eq.) in dry ethanol (15 mL). The resulting solution was stirred at 80 °C for 5 hours, when TLC showed complete consumption of starting material tosylate. The ethanol was removed *in vacuo* and the excess of benzylamine carefully removed by distillation under reduced pressure (Kugelrohr, 85 °C, 20 mmHg). The residue was partitioned between dichloromethane (60 mL) and 1.0 M aqueous sodium hydroxide solution (40 mL). The organic layer was separated, the aqueous layer extracted with dichloromethane (3 x 10 mL), the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (90% hexane 9% ethyl acetate 1% triethylamine) to give the *title compound* **1** (2.28 g, 9.75 mmol, 65%) as a colourless oil. ν_{max}(neat)/cm^{-1} 3313, 1606;δ_H (300 MHz; $CDCl_3$) 7.36-7.21 (5H, m, H-Ar), 6.29 (1H, td, *J* 7.0, 14.1, H-C3), 5.58 (1H, td, *J* 1.2, 14.1, H-C4), 3.81 (2H, s, H-C5), 2.70 (2H, t, *J* 7.0, H-C1), 2.35 (2H, ddt, *J* 1.2, 7.0, 7.0; H-C2), 1.36 (1H, bs, H-NH), 0.12 (9H, s, H-CTMS); δ_C (75.5 MHz; $CDCl_3$) 146.2 (C3), 140.5 (ArC), 131.2 (C4), 128.4 (ArCH), 128.1 (ArCH), 127.8 (ArCH), 54.0 (C5), 49.1 (C1), 34.1 (C2), 0.3 (CTMS).

(_Z_)-4-(Trimethylsilyl)but-3-en-1-amine (7)

NaN_3 (2.93 g, 45 mmol) was added portionwise to a solution of (*Z*)-4-(trimethylsilyl)but-3-en-1-yl 4-toluenesulfonate **6** (4.48 g, 15 mmol) in DMF (30 mL). The resulting solution was heated and stirred to 60 °C for 2 h. Work up was carried out based on general procedure **3**. Purification of the residue by flash column chromatography (PE:Et_2O 9:1) yielded the)-(4-azidobut-1-en-1-yl)trimethylsilane (2.29 g, 90%) as a colourless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ_H = 6.15 (1H, dt, *J* 14.2, 1.4), 5.50 (1H, dt, *J* 14.2, 7.3), 3.26 (2H, t, *J* 6.8), 2.26 (2H, qd, *J* 6.8, 1.4), 0.00 (9H, s); *m/z* (EI^+) 169 (1% $[M]^+$), 126 (25% $[C_4H_8N_3Si]^+$), 100 (50% $[C_4H_{10}NSi]^+$), 73 (100% $[C_3H_9Si]^+$).

A solution of $LiAlH_4$ (26.5 mL, 26.3 mmol; 1.0 M in THF) was diluted with THF (106 mL). After cooling to 0 °C, (*Z*)-(4-azidobut-1-en-1-yl)trimethylsilane (4.24 g, 25 mmol) in THF (25 mL) was added dropwise over 2 h using a syringe pump at a rate of 0.2 mmol per min. The mixture was stirred for 30 min at 0 °C and a solution of brine (4 mL per mmol) together with Et_2O (2 mL per mmol) was added dropwise over 30 min. The mixture was allowed to warm to rt over 30 min and any precipitate was removed by filtration through Celite®. The organic layer was separated and the aqueous layer extracted with Et_2O (3 x 1.2 mL per mmol). The combined organic solution were dried ($MgSO_4$), filtered, and volatile components removed under reduced pressure to yield the pure *title compound* (3.29 g, 92%) as a clear oil and this was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.28 (1H, dt, *J* 14.2, 6.9), 5.61 (1H, d, *J* 14.2), 2.76 (2H, t, *J* 6.9), 2.27 (2H, qd, *J* 6.9, 6.9), 1.21 (2H, bs), -0.13 (9H, s); *m/z* (EI^+) 99 (40% $[C_5H_{11}Si]^+$), 128 (50% $[C_7H_{16}Si]^+$), 74 (100% $[C_3H_{10}Si]^+$).

3-Buten-1-amine hydrochloride (8)

To a solution of 3-buten-1-ol (0.50 g, 6.93 mmol, 1 equiv.) in THF (11 mL) was added Ph_3P (1.99 g, 7.62 mmol, 1.1 equiv.) and phthalimide (1.12 g, 7.62 mmol, 1.1 equiv.) portionwise. This mixture was cooled to 0 °C and diisopropyl azodicarboxylate (1.5 mL, 7.62 mmol, 1.1 equiv.) was added dropwise over 2 min. The reaction mixture was stirred for 3 h at 0 °C before warming to rt overnight. *n*-Hexane (11 mL) was added and the suspension was filtered through Celite®. The filtrate was washed sequentially with aqueous HCl (12 mL; 1.0 M) and saturated aqueous $NaHCO_3$ (12 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (PE:EtOAc 9:1) afforded *N*-(but-3-enyl)phthalimide[37]a white solid (1.39 g, 100%). Mp 149-155 °C (lit mp 144 °C); ν_{max}(neat)/cm^{-1} 3021, 2927, 1708, 997, 956; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.70-7.55 (4H, m), 5.66 (1H, ddt, *J* 17.2, 10.5, 7.0), 4.95-4.86 (2H, m), 3.63 (2H, t, *J* 6.8), 2.32 (2H, q, *J* 7.0); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 168.0, 134.4, 133.7, 132.0, 123.0, 117.3, 37.2, 32.7; *m/z* (EI^+) 133 (15% $[(CO)_2C_6H_4^+]$), 201 (45% $[M^+]$).

To a solution of *N*-(but-3-enyl)phthalimide (1 g, 4.97 mmol) in 98% ethanol (25 mL) was added dropwise 98% hydrazine monohydrate (0.5 mL, 10 mmol) over 2 minutes. The mixture was heated to 50 °C and stirred under nitrogen for 1 h. During this time a white suspension formed and slowly solidified. After cooling to rt, HCl (5 mL, concentrated) was added dropwise over 3 minutes and the mixture was stirred for 10 minutes. The white precipitate was removed by filtration. After concentrating under reduced pressure, the residue was dissolved in water and the residues removed by filtration. The solvent was removed under reduced pressure to give the *title compound* **8** in quantitative yield as the HCl salt (0.53 g, 4.97 mmol). ν_{max}(neat)/cm^{-1} 3397, 2895, 1658, 998, 924;

^{1}H NMR (270 MHz, D_2O) δ_H = 5.82-5.67 (1H, m), 5.20-5.12 (2H, m), 3.04-2.99 (2H, t, *J* 6.7), 2.37 (2H, q, *J* 6.7); ^{13}C NMR (270 MHz, D_2O) δ_C = 133.3, 119.1, 38.7, 31.1. Treatment with dry triethylamine in dry dichloromethane followed by an aqueous was provided the free amine.

But-3-yn-1-amine[38]

To a cooled solution of 3-butyn-1-ol (5.40 mL, 71.34 mmol) in Et_2O (72 mL) were added MsCl (8.15 mL, 105.13 mmol) and Et_3N (1.5 mL, 105.13 mmol) at 0 °C and the solution gradually warmed to rt overnight. Work up was carried out based on general procedure **1**. Purification of the residues by flash column chromatography (PE:EtOAc 4:1) yielded but-3-yn-1-yl methanesulfonate[38] (8.39 g, 89%) as a clear oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 3288 (C4), 2941 (CH), 1334 (S=O), 1169 (S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.26 (2H, t, *J* 6.9), 3.02 (3H, s), 2.64-2.60 (2H, m), 2.05 (1H, t, *J* 2.6); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 78.9, 71.2, 67.5, 37.9, 20.1; *m/z* (EI$^+$) 149 (1% $[M]^+$), 109 (45% $[C_2H_5O_3S]^+$), 79 (100% $[CH_3O_2S]^+$). NaN_3 (7.80 g, 120 mmol) was added portionwise to a solution of but-3-yn-1-yl methanesulfonate (7.11 g, 47.97 mmol) in DMF (50 mL). The resulting solution was heated and stirred to 60 °C for 2 h. Work up was carried out based on general procedure **3**, and 4-azidobut-1-yne[38] (4.11 g, 90%) was isolated as a clear oil and used without purification. $\nu_{max}(CHCl_3)/cm^{-1}$ 3426, 2931, 2104; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.37 (2H, t, *J* 7.0), 2.43 (2H, td, *J* 7.0, 2.5), 2.02 (1H, t, *J* 2.5); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 80.4, 70.6, 49.8, 19.5.

To a cooled solution of $LiAlH_4$ (1.0 M in THF; 37.1 mL, 37.1 mmol) in THF (106 mL) was added 4-azidobut-1-yne (3.36 g, 35.33 mmol) in THF (35 mL) dropwise over 2 h at 0 °C. Work up was carried out based on general procedure **5**, and the *title compound* (0.49 g, 20%) was isolated as a clear oil and used without purification. $\nu_{max}(CHCl_3)/cm^{-1}$ 3410, 3293, 2924, 1556; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 2.84 (2H, t, *J* 6.2), 2.32 (2H, td, *J* 6.2, 2.6), 2.00 (1H, t, *J* 2.6), 1.51 (2H, bs); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 82.4, 69.7, 40.9, 23.4.

2. Cyclisation Precursors

***N*-(But-3-en-1-yl)-4,4-dimethoxybutanamide (11)**

According to General Procedure 2, to a stirred solution of 4,4-dimethoxybutanoic acid **9** (0.46 g, 3.10 mmol) and T3P® (50% in EtOAc; 2.12 mL, 3.57 mmol) in EtOAc (23 mL) were added sequentially Et_3N (0.86 mL, 6.20 mmol) and *N*-

homoallyl amine **5** (0.22 g, 3.10 mmol). After overnight stirring at rt, work up was carried out based on general procedure **2**, affording the *title compound* **11** (0.278 g, 65%) and this was used without any purification. ν_{max}(neat)/cm^{-1} 3011, 2937, 1688, 1457, 1173, 1080; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.76 (1H, ddt, *J* 17.1, 10.5, 6.6), 5.59 (1H, bs), 5.12-5.07 (2H, m), 4.38 (1H, t, *J* 5.4), 3.36-3.30 (2H, m), 3.33 (6H, s), 2.28-2.20 (4H, m), 1.96-1.91 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.4, 135.3, 117.0, 103.9, 53.2, 38.5, 33.3, 31.4, 28.4; *m/z* (EI$^+$) 131 (30% $[C_6H_{11}O_3]^+$), 71 (100% $[C_4H_8N]^+$); HRMS (NSI) Found (M+H$^+$) 202.1437, $C_{10}H_{20}NO_3$ requires 202.1438.

_N_-(But-3-en-1-yl)-5,5-dimethoxypentanamide (12)

According to General Procedure 2, to a solution of 5,5-dimethoxypentanoic acid **10** (1.17 g, 7.21 mmol) and T3P® (50% in EtOAc; 4.93 mL, 8.29 mmol) in EtOAc (54 mL) were added sequentially Et_3N (2.01 mL, 14.42 mmol) and *N*-homoallyl amine **5** (0.51 g, 7.21 mmol). After overnight stirring at rt, work up was carried out based on general procedure **2**, affording the *title compound* **12** (1.02 g, 66%) and this was used without any purification. ν_{max}(neat)/cm^{-1} 3296, 2936, 2831, 1642, 1126, 1051; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.75 (1H, ddt, *J* 17.1, 10.2, 6.9), 5.55 (1H, bs), 5.12-5.05 (2H, m), 4.35 (1H, t, *J* 5.4), 3.31 (2H, q, *J* 6.7), 3.31 (6H, s), 2.25 (2H, qt, *J* 6.8, 1.5), 2.18 (2H, t, *J* 7.3), 1.72-1.59 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.7, 135.5, 117.4, 104.7, 53.1, 38.5, 36.5, 34.0, 32.1, 21.0; *m/z* (EI$^+$) 215 (1% $[M]^+$), 184 (20% $[C_{10}H_{18}NO_2]^+$), 113 (35% $[C_6H_{10}NO]^+$), 71 (100% $[C_4H_8N]^+$); HRMS (NSI) Found (M+H$^+$) 216.1595, $C_{11}H_{22}NO_3$ requires 216.1594.

(*Z*)-4,4-Dimethoxy-*N*-(4-(trimethylsilyl)but-3-en-1-yl)butanamide (13)

According to General Procedure 2, to a solution of 4,4-dimethoxybutanoic acid **9** (0.20 mL, 1.33 mmol) and T3P® (50% in EtOAc; 0.91 mL, 1.53 mmol) in EtOAc (10 mL) were added sequentially Et_3N (0.37 mL, 2.66 mmol) and (*Z*)-4-(trimethylsilyl)but-3-en-1-amine **7** (0.19 g, 1.33 mmol). After overnight stirring at rt, work up was carried out based on general procedure **2**, affording the *title compound* **13** (0.15 g, 41%) and this was used without any purification. ν_{max}($CHCl_3$)/cm^{-1} 3296, 2955, 1647, 1250, 1061; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.22 (1H, dt, *J* 14.4, 7.3), 5.64 (1H, td, *J* 14.4, 1.3), 5.59 (1H, bs), 4.38 (1H, t, *J* 5.6), 3.39-3.24 (2H, m), 3.32 (6H, s), 2.33 (2H, q, *J* 6.7), 2.23-2.19 (2H, m), 1.96-1.91 (2H, m), 0.12 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.6, 144.9, 132.8, 104.1, 53.5, 39.2, 33.5, 31.7, 28.6, 0.5;

m/z (EI^+) 273 (1% $[M]^+$), 128 (50% $[C_6H_{14}NSi]^+$), 73 (65% $[C_3H_9Si]^+$), 71 (100% $[C_4H_8N]^+$); HRMS (APCI) Found ($M+H^+$) 274.1832, $C_{13}H_{28}NO_3Si$ requires 274.1833.

(*Z*)-5,5-Dimethoxy-*N*-(4-(trimethylsilyl)but-3-en-1-yl)pentanamide (14)

According to General Procedure 2, to a solution of 5,5-dimethoxypentanoic acid **10** (0.43 g, 2.65 mmol) and T3P® (50% in EtOAc; 1.82 mL, 3.05 mmol) in EtOAc (15 mL) were added sequentially Et_3N (0.74 mL, 5.30 mmol) and (*Z*)-4-(trimethylsilyl)but-3-en-1-amine 7 (0.38 g, 2.65 mmol). After overnight stirring at rt, work up was carried out based on general procedure **2**, affording the *title compound* **14** (0.39 g, 51%) and this was used without any purification. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 6.23 (1H, dt, *J* 14.2, 7.3), 5.65 (1H, dt, *J* 14.2, 1.3), 5.50 (1H, bs), 4.36 (1H, t, *J* 5.4), 3.35-3.30 (2H, m), 3.31 (6H, s), 2.33 (2H, qd, *J* 6.9, 1.3), 2.18 (2H, t, *J* 7.3), 1.73-1.60 (4H, m), 0.12 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.7, 145.0, 132.8, 104.7, 53.1, 39.1, 36.5, 33.6, 32.2, 21.0, 0.42; *m/z* (EI^+) 287 (1% $[M]^+$), 142 (35% $[C_7H_{16}NSi]^+$), 71 (100% $[C_4H_8N]^+$).

(*Z*)-5,5-Dimethoxy-*N*-(4-(trimethylsilyl)but-3-en-1-yl)pentanamine (16).

A solution of (*Z*)-5,5-dimethoxy-*N*-(4-(trimethylsilyl)but-3-en-1-yl)pentanamide (14) (575 mg, 2.00 mmol, 1.00 eq.) in tetrahydrofuran (4 mL) was added dropwise at room temperature to a stirred suspension of lithium aluminium hydride (80 mg, 2.10 mmol, 1.05 eq.) in tetrahydrofuran (4.2 mL). The reaction was heated to 60 °C for 5 hours. After this time the solution was cooled to room temperature and quenched with a saturated aqueous solution of sodium chloride (10 mL) and diluted with diethyl ether (5 mL). Aluminum salts were then removed by filtration through a pad of celite. The organic layer was separated and the aqueous layer extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The pale yellow residue was purified by a short flash column chromatography (100% ethyl acetate) to afford the *title compound* **16** (493 mg , 1.80 mmol, 90%) as a colourless oil. ν_{max}(neat)/cm^{-1} 3318, 2950, 2828, 1606, 857; δ_H (400 MHz; $CDCl_3$) 6.26 (1H, td, *J* 7.2, 14.4, H-C3), 5.57 (1H, td, *J* 1.2, 14.4, H-C4), 4.35 (1H, t, *J* 5.6, H-C9), 3.30 (6H, s, H-C10), 2.66 (2H, t, *J* 7.2, H-C1), 2.61 (2H, t, *J* 7.2, H-C5), 2.33 (2H, ddt, *J* 1.2, 7.2, 7.2, H-C2), 1.74 (1H, bs, H-NH), 1.63 (2H, m, H-C8), 1.55-1.48 (2H, m, H-C6), 1.40-1.33 (2H, m, H-C7), 0.11 (9H, s, H-CTMS); δ_C (100.6 MHz; $CDCl_3$) 146.3 (C3), 131.2 (C4), 104.5 (C9), 52.8 (C10), 50.0 (C5), 49.8 (C1),

34.1 (C2), 32.5 (C8), 30.0 (C6), 22.5 (C7), 0.3 (CTMS); *m/z* (CI) 274 (MH^+, 57), 242 (14), 86 (100); HRMS (CI) Found ($M+H^+$) 274.2202, $C_{14}H_{32}NO_2Si$ requires 274.2202.

_N_-(But-3-yn-1-yl)-4,4-dimethoxybutanamide (17)

To but-3-yn-1-amine (0.31 g, 4.48 mmol, 1 equiv.) in EtOAc (8 mL) was sequentially added 2,5-dioxopyrrolidin-1-yloxy 4,4-dimethoxybutanoate (1.10 g, 4.48 mmol, 1 equiv.) and *N*,*N*'-dicyclohexylcarbodiimide (0.93 g, 4.48 mmol, 1 equiv.) portionwise. The mixture was stirred at rt overnight and the precipitate was filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residues by flash column chromatography (EtOAc:CH_2Cl_2 1:4) yielded the *title compound* **16** (0.52 g, 59%) as a clear oil. ν_{max}(neat)/cm^{-1} 3291, 3084, 2939, 1721, 1125, 1054; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.12 (1H, bs), 4.35 (1H, t, *J* 5.3), 3.35 (2H, q, *J* 5.3), 3.29 (6H, bs), 2.37-2.34 (2H, m), 2.22 (2H, bt, *J* 7.3), 1.97 (1H, bt, *J* 2.5), 1.92-1.87 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.7, 104.1, 81.8, 70.1, 53.5, 38.1, 31.4, 28.4, 19.5; *m/z* (EI^+) 169 (20% $[C_9H_{15}NO_2]^+$), 125 (50% $[C_7H_{11}NO]^+$); HRMS (NSI) Found ($M+Na^+$) 222.1099, $C_{10}H_{17}NO_3Na$ requires 222.1101.

_N_-(But-3-yn-1-yl)-5,5-dimethoxypentanamide (18)

To a solution of 5,5-dimethoxypentanoic acid **10** (0.070 g, 0.43 mmol) and T3P® (50% in EtOAc; 0.29 mL, 0.49 mmol) in EtOAc (3.2 mL) were added sequentially Et_3N (0.12 mL, 0.86 mmol) and but-3-yn-1-amine (0.030 g, 0.43 mmol). After overnight stirring at rt, work up was carried out based on general procedure **2**, affording the *title compound* **17** (0.052 g, 57%) and this was used without any purification. ν_{max}(neat)/cm^{-1} 3308, 3011, 1666, 1257, 1166; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.89 (1H, bs), 4.35 (1H, t, *J* 5.4), 3.34 (2H, q, *J* 6.4), 3.31 (6H, s), 2.39 (2H, td, *J* 6.4, 2.6), 2.21 (2H, t, *J* 7.2), 2.00 (1H, t, *J* 2.6), 1.74-1.60 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.9, 104.6, 81.8, 70.1, 53.1, 38.1, 36.3, 32.0, 20.9, 19.7; *m/z* (EI^+) 213 (1% $[M]^+$); HRMS (NSI) Found ($M+H^+$) 214.1438, $C_{11}H_{20}NO_3$ requires 214.1438.

3. Aza-Silyl-Prins Inter- and Intramolecular Cyclisations

(±)-1-Benzyl-6-pentyl-1,2,3,6-tetrahydropyridine (3)[2]

Following the general procedure 4, *N*-benzyl-*N*-*Z*-(4-trimethylsilylbut-3-enyl)amine **1** (234 mg, 1.00 mmol), in the presence of 1,1-dimethoxyhexane (0.146 g, 172 μL, 1.00 mmol), disappeared on TLC after 12 hours of stirring at reflux temperature. The work up gave a brown oil, which was purified by flash column chromatography (96% hexane 3% ethyl acetate 1% triethylamine) to give the *title compound* **3** (182 mg, 75%) as a yellow oil. ν_{max}(neat)/cm^{-1} 3027, 2929, 2869, 1662; δ_H (400 MHz; $CDCl_3$) 7.37-7.24 (5H, m), 5.81-5.77 (1H, m), 5.65-5.61 (1H, m), 3.94 (1H, d, *J* 13.6), 3.40 (1H, d, *J* 13.6), 2.93-2.86 (2H, m), 2.40-2.36 (1H, m), 1.05-2.98 (2H, m), 1.63-1.55 (2H, m), 1.34-1.22 (6H, m), 0.89 (3H, t, *J* 6.5); δ_C (100.6 MHz; $CDCl_3$) 139.8, 130.2, 129.0, 128.2, 126.9, 125.1, 59.0, 58.2, 46.3, 33.4, 32.3, 25.1, 24.1, 22.8 , 14.2; *m/z* (CI) 244 (MH^+, 100), 172 (70), 120 (15); HRMS (CI) Found (MH^+) 244.2065, $C_{17}H_{26}N$ requires 244.2063.

Table 1 entry 2: 1,5,6,8a-Tetrahydroindolizin-3(2*H*)-one (19)[36]

According to General Procedure 4, a suspension of $Sc(OTf)_3$ (0.08 g, 0.16 mmol) in MeCN (3.5 mL) was heated to reflux for 5 min. A solution of (*Z*)-4,4-dimethoxy-*N*-(4-(trimethylsilyl)but-3-en-1-yl)butanamide **13** (0.05 g, 0.16 mmol) in MeCN (1.5 mL) was added dropwise over 1 min to the mixture. The suspension was stirred for 48 h. Work up was carried out based on general procedure 4. Purification of the residues by flash column chromatography (EtOAc:CH_2Cl_2 4:1) yielded the *title compound* **19** (0.0169 g, 75%) as a colourless oil. ν_{max}($CHCl_3$)/cm^{-1} 2927, 1665; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.79-5.75 (1H, m), 5.68-5.65 (1H, dm, *J* 10.2), 4.19 (1H, dd, *J* 13.4, 6.8), 4.12 (1H, bs), 2.84 (1H, td, *J* 12.3, 5.0), 2.50-2.34 (2H, m), 2.27-2.19 (2H, m), 2.08-2.02 (1H, dm, *J* 17.8), 1.63-1.53 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 173.2, 128.5, 125.2, 55.1, 36.4, 31.9, 26.5, 24.7; *m/z* (EI^+) 137 (100% $[M]^+$); HRMS (APCI) Found ($M+H^+$) 138.0914, $C_8H_{12}NO$ requires 138.0913.

Table 1 Entry 5: 2,3,6,7-Tetrahydro-1H-quinolizin-4(9a*H*)-one (20)[36]

According to General Procedure 4, a suspension of $Sc(OTf)_3$ (0.34 g, 0.70 mmol) in MeCN (3.5 mL) was heated to reflux for 5 min. A solution of (*Z*)-5,5-dimethoxy-*N*-(4-(trimethylsilyl)but-3-en-1-yl)pentanamide **14** (0.20 g, 0.70

mmol) in MeCN (1.5 mL) was added dropwise over 1 min to the mixture. The suspension was stirred for 48 h. Work up was carried out based on general procedure 4. Purification of the residues by flash column chromatography (EtOAc:CH_2Cl_2 1:1) yielded the *title compound* **20** (0.068 g, 64%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.84-5.79 (1H, m), 5.50 (1H, ddt, *J* 10.0, 2.8, 1.4), 4.81 (1H, ddt, *J* 12.5, 5.7, 1.1), 3.99-3.94 (1H, m), 2.58 (1H, td, *J* 12.5, 4.0), 2.50-2.43 (1H, m), 2.36-2.30 (1H, m), 2.28-2.18 (1H, m), 2.03-1.96 (2H, m), 1.87-1.80 (1H, m), 1.67 (1H, dddd, *J* 13.0, 5.6, 2.9, 1.1), 1.40 (1H, tdd, *J* 13.0, 11.4, 3.2); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 169.0, 129.1, 126.0, 55.3, 38.4, 32.6, 30.4, 25.3, 19.9; *m/z* (EI$^+$) 151 (100% $[M]^+$); HRMS (APCI) Found ($M+H^+$) 152.1069, $C_9H_{14}NO$ requires 152.1070.

4. Aza-Prins Intramolecular Cyclisations

Table 2 Entry 1: (7*R,8a*R**)-7-Chlorohexahydroindolizin-3(2*H*)-one (21a)**

According to General Procedure 5, *N*-(but-3-en-1-yl)-4,4-dimethoxybutanamide **11** (0.11 g, 0.55 mmol) was mixed with CH_2Cl_2 (5 mL) for 5 min and $FeCl_3$ (0.09 g, 0.55 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure 5. Purification of the residues by flash column chromatography (EtOAc:CH_2Cl_2 1:1) yielded the *title compound* **21a** (0.08 g, 94%) as a clear oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1673, 748; ^{1}H NMR (700 MHz, $CDCl_3$) δ_H = 4.16 (1H, dd, *J* 13.6, 5.1), 3.93 (1H, tt, *J* 12.0, 3.8), 3.48 (1H, dtd, *J* 11.0, 7.2, 3.4), 2.66 (1H, td, *J* 13.3, 3.1), 2.40-2.32 (3H, m), 2.24-2.19 (1H, m), 2.17-2.15 (1H, dm, *J* 13.3), 1.67-1.60 (2H, m), 1.49 (1H, q, *J* 12.0); ^{13}C NMR (176 MHz, $CDCl_3$) δ_C = 173.5, 56.5, 55.4, 43.9, 39.0, 35.3, 30.2, 24.6; *m/z* (EI$^+$) 173 (25% $[M]^+$), 138 (100% $[C_8H_{12}NO]^+$); HRMS (NSI) Found ($M+H^+$) 174.0679, $C_8H_{13}{}^{35}ClNO$ requires 174.0680.

Table 2 Entry 3: (7*R,8a*R**)-7-Bromohexahydroindolizin-3(2*H*)-one (21b)**

According to General Procedure 5, *N*-(but-3-en-1-yl)-4,4-dimethoxybutanamide **11** (0.13 g, 0.63 mmol) was mixed with CH_2Br_2 (5 mL) for 5 min and BBr_3 (1.0 M in CH_2Cl_2; 0.63 g, 0.63 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure **5**. Purification of the residues by flash column chromatography (EtOAc:CH_2Cl_2 1:1) yielded the *title compound* **21b** (0.070 g, 51%) as a clear oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1673, 651; ^{1}H NMR (400

MHz, $CDCl_3$) δ_H = 4.05-4.00 (1H, m), 3.94 (1H, dtd, *J* 10.8, 7.4, 3.5), 3.12 (1H, td, *J* 12.8, 3.3), 2.41-2.36 (1H, m), 2.28-2.22 (2H, m), 2.02-1.99 (1H, m), 1.86-1.80 (1H, m), 1.67-1.56 (3H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 173.8, 52.0, 49.8, 41.0, 35.6, 32.6, 29.1, 24.5; *m/z* (EI^+) 217 (5% $[M-H]^+$), 138 (100% $[C_8H_{12}NO]^+$); HRMS (EI) Found (M^+) 217.0096, $C_8H_{12}{}^{79}BrNO$ requires 217.0097.

Table 2 Entry 5: C*is* and *Trans* 7-Fluorohexahydroindolizin-3(2*H*)-one (21c)

N-(But-3-en-1-yl)-4,4-dimethoxybutanamide **11** (0.20 g, 0.99 mmol) was mixed with PhH (5 mL) for 5 min and $BF_3.OEt_2$ (0.13 mL, 0.99 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure **5**. Purification of the residues by flash column chromatography (EtOAc:CH_2Cl_2 1:1) yielded a mixture of the *title compound*s (0.056 g, 36%) as a clear oil, in a mixture of diastereomers of ratio 1:1. ν_{max}($CHCl_3$)/cm^{-1} 1677, 1422; ***cis*- isomer** (**7*R**,8a*R**)-7-Fluorohexahydroindolizin-3(2*H*)-one** ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.02-4.88 (1H, dm, J_{HF} 47.0), 4.15 (1H, dddd, *J* 13.8, 5.7, 3.8, 1.5), 3.49-3.42 (1H, m), 2.62-2.55 (1H, tm, *J* 13.2), 2.37-2.30 (1H, m), 2.23-2.15 (3H, m), 1.96 (1H, ddtd, *J* 16.5, 7.6, 3.8, 1.6), 1.67-1.57 (1H, m), 1.54-1.42 (1H, m), 1.38-1.20 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 173.8, 87.1 (d, J_{CF} 169.6), 51.4, 38.1 (d, J_{CF} 20.9), 36.8 (d, J_{CF} 13.9), 30.3), 29.4 (d, J_{CF} 20.6), 25.1; ***trans*- isomer** (**7*R**,8a*S**)-7-Fluorohexahydroindolizin-3(2*H*)-one** ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.58 (1H, dtt, J_{HF} 47.8, 11.3, 4.4), 3.98 (1H, ddd, *J* 13.8, 6.1, 1.1), 3.75 (1H, dtd, *J* 11.5, 7.1, 3.7), 2.95 (1H, dt, *J* 13.3, 3.6), 2.37-2.30 (2H, m), 2.28-2.24 (1H, m), 2.11-2.03 (1H, m), 1.67-1.57 (1H, m), 1.54-1.42 (2H, m), 1.38-1.20 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 173.6, 89.7 (d, J_{CF} 175.8), 55.1 (d, J_{CF} 12.5), 39.5 (d, J_{CF} 18.1), 34.6 (d, J_{CF} 2.1), 31.2 (d, J_{CF} 19.5), 30.4, 24.7; ^{19}F NMR (377 MHz, $CDCl_3$), δ_F = −173.0 and −189.7; *m/z* (EI^+) 157 (100% $[M]^+$); HRMS (APCI) Found ($M+H^+$) 158.0973, $C_8H_{13}FNO$ requires 158.0976.

Table 2 Entry 8: (8*R,9a*R**)-8-Chlorohexahydro-1H-quinolizin-4(6*H*)-one (22a)**

N-(But-3-en-1-yl)-5,5-dimethoxypentanamide **12** (0.21 g, 0.99 mmol) was mixed with CH_2Cl_2 (5 mL) for 5 min and $FeCl_3$ (0.16 g, 0.99 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure **5**. Purification of the residues by flash column chromatography (EtOAc:CH_2Cl_2 1:1) yielded the *title compound* **22a** (0.16 g, 86%) as a clear oil. ν_{max}($CHCl_3$)/cm^{-1} 1626, 745; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H = 4.80 (1H, ddd, *J* 13.7, 4.6, 2.5), 3.93 (1H, tt, *J* 11.8, 4.4), 3.27 (1H, dddd, *J* 11.3, 8.4, 5.6, 2.4), 2.42 (1H, td, *J* 13.7, 2.7), 2.40-2.34 (1H, dtm, *J* 17.1, 5.0), 2.29

(1H, ddd, *J* 17.4, 9.6, 5.6), 2.20-2.13 (2H, m), 1.99-1.95 (1H, m), 1.82-1.77 (1H, m), 1.68-1.57 (3H, m), 1.51 (1H, dddd, *J* 19.0, 11.1, 8.1, 3.2); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 169.6, 56.1, 56.0, 44.3, 41.7, 36.2, 33.1, 30.2, 19.6; *m/z* (EI^+) 187 (25% $[M]^+$), 152 (100% $[C_9H_{14}NO]^+$); HRMS (EI) Found (M^+) 187.0759, $C_9H_{14}{}^{35}ClNO$ requires 187.0758.

Table 2 Entry 10: (8*R,9a*R**)-8-Bromohexahydro-1*H*-quinolizin-4(6*H*)-one (22b)**

N-(But-3-en-1-yl)-5,5-dimethoxypentanamide **12** (0.21 g, 0.99 mmol) was mixed with CH_2Br_2 (5 mL) for 5 min and $InBr_3$ (0.55 g, 0.99 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure **5**. Purification of the residues by flash column chromatography (EtOAc:CH_2Cl_2 1:1) yielded the *title compound* **22b** (0.22 g, 86%). ν_{max}($CHCl_3$)/cm^{-1} 1628, 647; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.73 (1H, ddd, *J* 13.8, 4.7, 2.6), 4.03 (1H, tt, *J* 12.1, 4.4), 3.24 (1H, dddd, *J* 11.2, 8.3, 5.5, 2.4), 2.40 (1H, td, *J* 13.5, 2.7), 2.35-2.20 (4H, m, H-C3, H-C7 and H-C9), 1.97-1.91 (1H, m), 1.81-1.74 (3H, m), 1.69-1.57 (1H, m), 1.53-1.42 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 169.4, 56.9, 46.7, 44.9, 42.6, 36.9, 32.9, 29.9, 19.3; *m/z* (EI^+) 232 (5% $[M]^+$), 152 (100% $[C_9H_{14}NO]^+$); HRMS (APCI) Found ($M+H^+$) 232.0332, $C_9H_{15}{}^{79}BrNO$ requires 232.0332.

Table 2 Entry 11: *Cis*- and *trans* 8-Fluorohexahydro-1*H*-quinolizin-4(6*H*)-one (22c)

N-(But-3-en-1-yl)-5,5-dimethoxypentanamide **12** (0.21 g, 0.99 mmol) was mixed with PhH (5 mL) for 5 min and BF_3.OEt_2 (0.13 mL, 0.99 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure **5**. Purification of the residues by flash column chromatography (EtOAc:$CHCl_3$ 2:3) yielded a mixture of the *title compound*s and its isomer (0.056 g, 33%) as a colourless oil. ν_{max}($CHCl_3$)/cm^{-1} 1617, 1419, 1267; ***cis*- isomer (8*R**,9a*R**)-8-fluorohexahydro-1*H*-quinolizin-4(6*H*)-one** ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.65 (1H, ddd, *J* 13.5, 5.4, 1.7), 4.63 (1H, dtt, J_{HF} 48.8, 11.0, 4.9), 3.31-3.24 (1H, m), 2.81 (1H, td, *J* 13.5, 2.8), 2.39-2.27 (2H, m), 2.18-2.06 (2H, m), 2.05-1.95 (2H, m), 1.87-1.76 (1H, m), 1.73-1.65 (1H, m), 1.61-1.55 (1H, m), 1.54-1.42 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 169.6, 89.8 (d, J_{CF} 176.3), 54.0 (d, J_{CF} 12.7), 40.1 (d, J_{CF} 16.3), 36.5, 33.0, 32.0 (d, J_{CF} 18.6), 30.3, 19.2; ***trans*- isomer (8*R**,9a*S**)-8-fluorohexahydro-1*H*-quinolizin-4(6*H*)-one** ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.03-4.89 (1H, dm, J_{HF} 47.9), 4.85 (1H, dtd, *J* 13.8, 4.8, 2.7), 3.69-3.62 (1H, m), 2.46-2.39 (1H, m), 2.39-2.27 (2H, m), 2.18-2.06 (1H, m), 2.05-1.95 (2H, m), 1.87-1.76 (2H, m), 1.61-1.55 (2H, m), 1.54-1.42 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 169.6, 87.1 (d, J_{CF} 168.8), 50.8, 39.5 (d, J_{CF} 13.0), 38.6 (d, J_{CF} 20.6), 33.1, 30.3 (d, J_{CF} 20.8), 29.9,

19.6; ^{19}F NMR (377 MHz, $CDCl_3$), δ_F = −172.0 and −187.1; *m/z* (EI$^+$) 151 (45% $[C_9H_{15}FN]^+$), 171 (80% $[M]^+$); HRMS (APCI) Found (M+H$^+$) 172.1131, $C_9H_{15}FNO$ requires 172.1132.

1-(But-3-yn-1-yl)-5-methoxypyrrolidin-2'-one (28)

N-(But-3-yn-1-yl)-4,4-dimethoxybutanamide **17** (0.07 g, 0.37 mmol) was mixed with CH_2Cl_2 (5 mL) for 5 min and $FeCl_3$ (0.06 g, 0.37 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure **5**. Purification of the residues by flash column chromatography (EtOAc:CH_2Cl_2 1:1) yielded the *title compound* **28** (0.015 g, 24%) as a clear oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 3289, 2942, 1660, 1283; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.08 (1H, dd, *J* 6.3, 1.3), 3.64 (1H, ddd, *J* 14.0, 7.6, 5.7), 3.32 (1H, dt, *J* 14.0, 7.6), 3.28 (3H, s), 2.58-2.46 (2H, m), 2.46-2.38 (1H, m), 2.33 (1H, ddd, *J* 16.7, 10.0, 3.0), 2.21-2.11 (1H, m), 2.03-1.99 (1H, dm, *J* 9.7), 1.97 (1H, t, *J* 2.7); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 175.3, 90.9, 81.8, 69.9, 53.2, 39.7, 29.0, 24.1, 18.2; *m/z* (EI$^+$) 167 (25% $[M]^+$), 68 (100% $[C_4H_6N]^+$); HRMS (APCI) Found (M+H$^+$) 168.1018, $C_9H_{14}NO_2$ requires 168.1019.

1-(But-3-yn-1-yl)-5-methoxy-1H-pyrrol-2'(5H)-one (29)

N-(But-3-yn-1-yl)-4,4-dimethoxybutanamide **17** (0.074 g, 0.37 mmol) was mixed with CH_2Cl_2 (5 mL) for 5 min and $FeCl_3$ (0.060 g, 0.37 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure **5**. Purification of the residues by flash column chromatography (EtOAc:CH_2Cl_2 1:1) yielded the *title compound* **29** (0.0024 g, 4%) as a clear oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 3286, 2932, 1697, 1093; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.90 (1H, dd, *J* 6.1, 1.6), 6.28 (1H, dd, *J* 6.1, 0.9), 5.64 (1H, bs), 3.75 (1H, ddd, *J* 13.6, 7.1, 5.9), 3.34 (1H, dt, *J* 13.6, 7.1), 3.12 (3H, s), 2.60-2.43 (2H, m), 1.98 (1H, t, *J* 2.7); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 173.7, 144.0, 130.7, 88.7, 81.5, 70.2, 50.8, 38.3, 18.6; *m/z* (EI$^+$) 150 (5% $[C_9H_{11}NO]^+$), 96 (75% $[C_7H_6NO]^+$); HRMS (APCI) Found (M+H$^+$) 166.0860, $C_9H_{12}NO_2$ requires 166.0863.

1-(But-3-en-1-yl)-5-methoxypyrrolidin-2'-one (26)

N-(But-3-en-1-yl)-4,4-dimethoxybutanamide **15** (0.20 g, 0.99 mmol) was mixed with CH_2Cl_2 (5 mL) for 5 min and $InCl_3$ (0.35 g, 0.99 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure

5. Purification of the residues by flash column chromatography (EtOAc:CH_2Cl_2 1:1) yielded the *title compound* **26** (0.025 g, 15%) as a clear oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 3009, 1696, 1079; ^1H NMR (400 MHz, $CDCl_3$) δ_H = 5.76 (1H, ddt, *J* 17.1, 10.3, 6.8), 5.10-5.00 (2H, m), 4.94 (1H, dd, *J* 6.4, 1.4), 3.59 (1H, ddd, *J* 13.8, 8.0, 7.1), 3.25 (3H, s), 3.17-3.10 (1H, m), 2.49 (1H, dd, *J* 17.5, 8.8), 2.36-2.26 (3H, m), 2.10 (1H, ddd, *J* 10.0, 8.5, 6.4), 1.97 (1H, ddd, *J* 14.2, 3.2, 1.4); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 175.3, 135.5, 117.0, 90.3, 52.8, 40.0, 32.2, 29.2, 23.9; *m/z* (EI^+) 169 (5% $[M]^+$), 138 (25% $[C_8H_{12}NO]^+$), 68 (100% $[C_4H_6N]^+$); HRMS (EI) Found (M^+) 169.1096, $C_9H_{15}NO_2$ requires 169.1097.

1-(But-3-en-1-yl)-5-hydroxypyrrolidin-2'-one (27)

N-(But-3-en-1-yl)-4,4-dimethoxybutanamide **15** (0.20 g, 0.99 mmol) was mixed with CH_2Cl_2 (5 mL) for 5 min and $InCl_3$ (0.35 g, 0.99 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure **5**. Purification of the residues by flash column chromatography (EtOAc:CH_2Cl_2 1:1) yielded the *title compound* **27** (0.011 g, 7%) as a clear oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 3344, 2979, 1667, 1464; ^1H NMR (600 MHz, $CDCl_3$) δ_H = 5.77 (1H, ddt, *J* 17.1, 10.2, 7.0), 5.22-5.20 (1H, m), 5.08 (1H, dt, *J* 17.1, 1.6), 5.05-5.03 (1H, dm, *J* 10.2), 3.54 (1H, dt, *J* 13.8, 7.5), 3.28-3.23 (1H, dm, 13.8), 3.41 (1H, d, *J* 8.1), 2.58-2.51 (1H, m), 2.38-2.26 (4H, m), 1.91-1.87 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 175.0, 135.7, 117.2, 83.6, 39.6, 32.4, 29.1, 28.6; *m/z* (EI^+) 68 (45% $[C_4H_6N]^+$), 137 (25% $[C_8H_{11}NO]^+$), 96 (100% $[C_5H_6NO]^+$); HRMS (EI) Found (M^+-H_2O) 137.0834, $C_8H_{11}NO$ requires 137.0835.

Table 3 Entry 1: (7*R,8a*R**)-7-Phenylhexahydroindolizin-3(2*H*)-one (30a)[21]**

N-(But-3-en-1-yl)-4,4-dimethoxybutanamide **11** (0.20 g, 0.99 mmol) was mixed with PhH (5 mL) for 5 min and $BF_3.OEt_2$ (0.13 mL, 0.99 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure **5**. Purification of the residues by flash column chromatography (EtOAc:CH_2Cl_2 1:1) yielded the *title compound* **30a** (0.043 g, 20%) as a clear oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 2936, 1672; ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.33-7.29 (2H, m), 7.23-7.17 (3H, m), 4.25 (1H, ddd, *J* 13.4, 5.0, 1.8), 3.59 (1H, dtd, *J* 10.9, 7.3, 3.5), 2.79 (1H, td, *J* 13.0, 3.5), 2.72 (1H, dt, *J* 12.4, 3.2), 2.43-2.38 (2H, m), 2.29-2.20 (1H, m), 2.09-2.04 (1H, dm, *J* 12.9), 1.90-1.85 (1H, dm, *J* 13.3), 1.69-1.61 (1H, m), 1.57 (1H, qd, *J* 12.7, 4.9), 1.38 (1H, q, *J* 12.0); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 173.7, 145.2, 128.8, 126.8, 126.7, 57.4, 42.1, 41.2,

40.1, 32.2, 30.5, 25.3; *m/z* (EI^+) 137 (45% $[C_8H_{11}NO]^+$), 215 (60% $[M]^+$); HRMS (NSI) Found ($M+H^+$) 216.1382, $C_{14}H_{18}NO$ requires 216.1383.

Table 3 Entry 2: (7*R,8a*R**)-*N*-(3-Oxooctahydroindolizin-7-yl)acetamide (30b)[21]**

N-(But-3-en-1-yl)-4,4-dimethoxybutanamide **11** (0.14 g, 0.69 mmol) was mixed with MeCN (5 mL) for 5 min and $BF_3.OEt_2$ (0.09 mL, 0.69 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure **5**, the *title compound* **30b** (0.003 g, 2%) was isolated as a clear oil without purification. $\nu_{max}(CHCl_3)/cm^{-1}$ 3293, 1656; ^1H NMR (400 MHz, $CDCl_3$) δ_H = 5.33 (1H, bs), 4.17 (1H, ddd, *J* 13.4, 5.2, 1.9), 3.99 (1H, dtt, *J* 15.7, 11.8, 3.9), 3.57 (1H, dtd, *J* 10.9, 7.5, 3.3), 2.75 (1H, td, *J* 13.4, 3.4), 2.40-2.36 (2H, m), 2.27-2.26 (1H, m), 2.24-2.19 (1H, m), 1.98 (3H, s), 1.99-1.93 (1H, m), 1.64-1.55 (1H, m), 1.26-1.17 (1H, m), 1.02 (1H, q, *J* 11.5); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 173.7, 169.7, 56.0, 46.7, 40.3, 38.5, 31.3, 30.4, 24.9, 23.7; *m/z* (EI^+) 196 (65% $[M]^+$), 137 (100% $[C_8H_{11}NO]^+$); HRMS (EI) Found (M^+) 196.1204, $C_{10}H_{16}N_2O_2$ requires 196.1206.

Table 3 Entry 2: (7*R,8a*R**)-7-Aminohexahydroindolizin-3(2*H*)-one (30c)**

N-(But-3-en-1-yl)-4,4-dimethoxybutanamide **11** (0.14 g, 0.69 mmol) was mixed with MeCN (5 mL) for 5 min and $BF_3.OEt_2$ (0.09 mL, 0.69 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure **5**. Upon separation from the organic layer, the aqueous layer was saturated by the addition of K_2CO_3, and extracted with $CHCl_3$ (3 x 4 mL). The $CHCl_3$ extracts were combined and washed with brine (4 mL), dried ($MgSO_4$), filtered, and volatiles were evaporated under reduced pressure to yield the *title compound* **30c** (0.043 g, 40%) as a clear oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 3300 (NH), 3286 (NH), 1663 (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 4.13 (1H, ddd, *J* 13.4, 5.2, 1.8), 3.48 (1H, dtd, *J* 10.8, 7.4, 3.4), 2.86 (1H, tt, *J* 11.3, 3.7), 2.65 (1H, td, *J* 13.4, 3.3), 2.39-2.34 (2H, m), 2.24-2.16 (1H, m), 2.05-2.00 (1H, dm, *J* 12.6), 1.86-1.80 (1H, dm, *J* 12.8), 1.65-1.55 (1H, m), 1.34 (2H, bs), 1.23-1.11 (1H, m), 1.05-0.94 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 173.7, 56.3, 48.8, 43.7, 38.6, 35.0, 30.6, 25.1; *m/z* (EI^+) 137 (35% $[C_8H_{11}NO]^+$), 154 (50% $[M]^+$); HRMS (NSI) Found ($M+H^+$) 155.1177, $C_8H_{15}N_2O$ requires 155.1179.

Table 3 Entry 3: (7*R,8a*R**)-3-Oxooctahydroindolizin-7-yl acetate (30d)[39]**

N-(But-3-en-1-yl)-4,4-dimethoxybutanamide **11** (0.20 g, 0.99 mmol) was mixed with EtOAc (5 mL) for 5 min and $BF_3.OEt_2$ (0.13 mL, 0.99 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure **5**. Purification of the residues by flash column chromatography (EtOAc:CH_2Cl_2 1:1) yielded the *title compound* **30d** (0.07 g, 40%) as a clear oil, which slowly crystallised. $\nu_{max}(CHCl_3)/cm^{-1}$ 1730, 1683, 1241; ^1H NMR (400 MHz, $CDCl_3$) δ_H = 4.86 (1H, tt, *J* 11.4, 4.2), 4.20 (1H, ddd, *J* 13.5, 5.2, 1.9), 3.57 (1H, dtd, *J* 10.9, 7.5, 3.3), 2.72 (1H, td, *J* 13.5, 3.4), 2.42-2.37 (2H, m), 2.28-2.19 (2H, m), 2.05 (3H, s), 2.03-1.97 (1H, dm, *J* 12.5), 1.69-1.61 (1H, m), 1.49-1.39 (1H, m), 1.33-1.19 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 173.6, 170.6, 70.6, 55.4, 39.0, 37.6, 30.4, 30.2, 24.8, 21.4; *m/z* (EI^+) 197 (25% $[M]^+$), 137 (100% $[C_8H_{11}NO]^+$); HRMS (APCI) Found ($M+H^+$) 198.1124, $C_{10}H_{16}NO_3$ requires 198.1125. Deposited with Cambridge Crystallographic Data Collection 1032728.

Table 3 Entry 4: (8*R,9a*R**)-8-Phenylhexahydro-1H-quinolizin-4(6*H*)-one (31a)[21]**

N-(But-3-en-1-yl)-5,5-dimethoxypentanamide **12** (0.21 g, 0.99 mmol) was mixed with PhH (5 mL) for 5 min and $BF_3.OEt_2$ (0.13 mL, 0.99 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure **5**. Purification of the residues by flash column chromatography (EtOAc:$CHCl_3$ 2:3) yielded the *title compound* **31a** (0.052 g, 23%) as a colourless oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 2997, 1622; ^1H NMR (600 MHz, $CDCl_3$) δ_H = 7.33-7.28 (2H, m), 7.23-7.18 (3H, m), 4.92 (1H, ddd, *J* 13.3, 4.2, 2.4), 3.40 (1H, dddd, *J* 11.2, 8.4, 5.5, 2.5), 2.76 (1H, tt, *J* 12.3, 3.6), 2.58 (1H, td, *J* 13.3, 2.7), 2.45 (1H, dtm, *J* 17.5, 5.3), 2.37 (1H, ddd, *J* 17.5, 9.8, 5.5), 2.02 (1H, ddtd, *J* 13.4, 5.9, 3.1, 1.6), 1.95-1.87 (2H, m), 1.87-1.80 (1H, m), 1.75-1.63 (1H, m), 1.63-1.45 (3H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 169.5, 145.3, 128.8, 126.9, 126.7, 56.8, 42.8, 42.4, 41.9, 33.2, 32.8, 30.6, 19.5; *m/z* (EI^+) 151 (85% $[C_{15}H_{20}N]^+$), 229 (100% $[M]^+$); HRMS (APCI) Found ($M+H^+$) 230.1539, $C_{15}H_{20}NO$ requires 230.1539.

Table 3 Entry 5: (8*R,9a*R**)-*N*-(6-oxooctahydro-1*H*-quinolizin-2-yl)acetamide (31b)[21]**

N-(But-3-en-1-yl)-5,5-dimethoxypentanamide **12** (0.21 g, 0.99 mmol) was mixed with MeCN (5 mL) for 5 min and $BF_3.OEt_2$ (0.13 mL, 0.99 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure **5**. Purification of the residues by flash column chromatography (EtOAc:$CHCl_3$ 2:3) yielded the *title compound* **31b** (0.0012 g, 1%) as a colourless oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 3287, 1621; ^1H NMR (600 MHz, $CDCl_3$) δ_H = 5.29 (1H, bs), 4.84 (1H, ddd, *J* 13.5, 4.7, 2.6), 3.99 (1H, tt, *J* 11.8, 4.3), 3.38-3.33 (1H, m), 2.52 (1H, td, *J* 13.5, 2.8), 2.42 (1H, dtm, *J* 17.1,

5.4), 2.32 (1H, ddd, *J* 17.1, 10.2, 5.7), 2.12-2.09 (1H, dm, *J* 13.0), 2.01-1.95 (2H, m), 1.97 (3H, s), 1.84-1.78 (1H, m), 1.71-1.67 (1H, m), 1.53-1.47 (1H, m), 1.30-1.21 (1H, m), 1.12 (1H, q, *J* 12.0); ^{13}C NMR (151 MHz, $CDCl_3$) δ_C = 169.7, 169.6, 55.3, 47.2, 41.0, 40.6, 32.0, 30.3, 33.1, 23.7, 19.5; *m/z* (EI^+) 210 (45% $[M]^+$), 151 (100% $[C_9H_{13}NO]^+$); HRMS (EI) Found (M^+) 210.1365, $C_{11}H_{18}N_2O_2$ requires 210.1363.

Table 3 Entry 6: (8*R,9a*R**)-6-Oxooctahydro-1*H*-quinolizin-2-yl acetate (31c)**

N-(But-3-en-1-yl)-5,5-dimethoxypentanamide **12** (0.21 g, 0.99 mmol) was mixed with EtOAc (5 mL) for 5 min and $BF_3.OEt_2$ (0.13 mL, 0.99 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure 5. Purification of the residues by flash column chromatography (EtOAc:$CHCl_3$ 2:3) yielded the *title compound* **31c** (0.008 g, 4%) as a colourless oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1734, 1638, 1244; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.88-4.80 (2H, m), 3.35 (1H, dddd, *J* 11.4, 8.1, 5.5, 2.6), 2.50 (1H, td, *J* 13.6, 2.6), 2.42 (1H, dtm, *J* 17.5, 5.0), 2.32 (1H, ddd, *J* 17.5, 9.6, 5.4), 2.10-2.09 (1H, m), 2.07-1.97 (2H, m), 2.04 (3H, s), 1.88-1.79 (1H, m), 1.74-1.67 (1H, m), 1.54 (1H, dtd, *J* 13.5, 8.0, 2.7), 1.49-1.40 (1H, m), 1.38 (1H, q, *J* 11.7); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 170.7, 169.6, 71.0, 54.6, 40.2, 39.3, 31.0, 30.3, 33.1, 21.4, 19.6; *m/z* (EI^+) 211 (50% $[M]^+$), 151 (75% $[C_9H_{13}NO]^+$); HRMS (EI) Found (M^+) 211.1204, $C_{11}H_{17}NO_3$ requires 211.1203.

Table 3 Entry 6: (8*R,9a*R**)-8-Hydroxyhexahydro-1H-quinolizin-4(6*H*)-one (31d)**

N-(But-3-en-1-yl)-5,5-dimethoxypentanamide **12** (0.21 g, 0.99 mmol) was mixed with EtOAc (5 mL) for 5 min and $BF_3.OEt_2$ (0.13 mL, 0.99 mmol) was added. The mixture was stirred for 48 h. Work up was carried out based on general procedure **5**. Upon separation from the organic layer, the aqueous layer was extracted with EtOAc (3 x 4 mL). The EtOAc extracts were combined and washed with brine (4 mL), dried ($MgSO_4$), filtered, and volatiles were evaporated under reduced pressure to yield the *title compound* **31d** (0.009 g, 6%) as a colourless oil without purification. $\nu_{max}(CHCl_3)/cm^{-1}$ 3365, 1615; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H = 4.82 (1H, ddd, *J* 13.7, 4.7, 2.6), 3.79 (1H, tt, *J* 11.1, 4.5), 3.28 (1H, dtd, *J* 14.1, 5.6, 2.6), 2.45 (1H, td, *J* 13.7, 2.7), 2.41-2.29 (2H, m), 2.05-1.96 (3H, m), 1.88-1.79 (1H, m), 1.75-1.63 (1H, m), 1.60-1.51 (1H, m), 1.74 (1H, bs), 1.41-1.24 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 169.7, 69.0, 54.5, 43.1, 40.4, 34.8, 33.1, 30.4, 19.6; *m/z* (EI^+) 169 (75% $[M]^+$), 154 (50% $[C_9H_{16}NO]^+$); HRMS (APCI) Found ($M+H^+$) 170.1175, $C_9H_{16}NO_2$ requires 170.1176.

2,3,9,9a-Tetrahydro-1*H*-quinolizin-4(8*H*)-one (23b)[40]

A suspension of $BF_3.OEt_2$ (0.08 mL, 0.63 mmol) in cyclohexane (3.5 mL) was heated to reflux for 5 min. A solution of (*Z*)-5,5-dimethoxy-*N*-(4-(trimethylsilyl)but-3-en-1-yl)pentamide (0.14 g, 0.63 mmol) in cyclohexane (1.5 mL) was added dropwise over 1 min to the mixture. The suspension was stirred at reflux for 48 h. The solution was cooled to room temperature, poured into a biphasic solution of CH_2Cl_2 (4 mL per mmol) and water (8 mL per mmol) and stirred for 30 min. The organic layer was separated and the aqueous later extracted with CH_2Cl_2. The combined organic fractions were washed with brine (4 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:CH_2Cl_2, 2:3) to give the *title compound* **23b** in a 1:1 inseparable mixture with **19** (**23a**) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.78-5.72 (1H, m), 5.69-5.64 (1H, m), 4.73-4.68 (1H, m), 3.46-3.41 (1H, m), 3.31-3.24 (1H, m), 2.39-2.36 (4H, m), 2.02-1.95 (2H, m), 1.84-1.77 (1H, m), 1.72-1.65 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 169.8, 124.4, 124.3, 52.8, 42.4, 33.1, 33.0, 29.3, 18.6.

2,3,9,9a-Tetrahydro-1*H*-quinolizin-4(8*H*)-one (23c)[41]

A suspension of $BF_3.OEt_2$ (0.08 mL, 0.63 mmol) in cyclohexane (3.5 mL) was heated to reflux for 5 min. A solution of (*Z*)-5,5-dimethoxy-*N*-(4-(trimethylsilyl)but-3-en-1-yl)pentanamide **13** (0.14 g, 0.63 mmol) in cyclohexane (1.5 mL) was added dropwise over 1 min to the mixture. The suspension was stirred for 48 h. Work up was carried out based on general procedure **5**. Purification of the residues by flash column chromatography (EtOAc:CH_2Cl_2 2:3) yielded the *title compound* **23c** (0.10 g, 18%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.25 (1H, dm, *J* 8.4), 5.12 (1H, dd, *J* 8.4, 1.4), 3.43 (1H, tm, *J* 11.4), 2.54 (1H, ddt, *J* = 18.0, 5.5, 2.1), 2.38 (1H, ddd, *J* = 18.0, 12.1, 6.5), 2.19 (1H, m), 2.08 (1H, tt, *J* 5.5, 1.5), 2.02-1.86 (3H, m), 1.73 (1H, ddd, *J* 13.2, 5.5, 2.9), 1.63-1.45 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 161.8, 124.0, 109.8, 55.5, 32.7, 30.5, 30.3, 22.3, 20.2; *m/z* (EI$^+$) 151 (100% $[M]^+$); HRMS (APCI) Found ($M+H^+$) 152.1067, $C_9H_{14}NO$ requires 152.1070.

ASSOCIATED CONTENT

Supporting information: [Experimental details for starting materials, copies of spectra for all novel compounds and X-ray crystallographic data]. This material is available free of charge via the Internet at http://pubs.acs.org/

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Notes

The authors declare no competing financial interest.

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