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Abstract

Novel tricyclic bridged heterocyclic systems can be readily prepared from sequential 1,4- and 1,2-addition reactions of allyl and 3-substituted allylsilanes to indolizidine and quinolizidine α,β-unsaturated N-acyliminium ions. These reactions involve a novel N-assisted, transannular 1,5-hydride shift. Such a mechanism was supported by examining the reaction of a dideuterated indolizidine, α,β-unsaturated N-acyliminium ion precursor, which provided specifically dideuterated tricyclic bridged heterocyclic products, and from computational studies. In contrast, the corresponding pyrrolo[1,2-a]azepine system did not provide the corresponding tricyclic bridged heterocyclic product and gave only a bis-allyl adduct, while more substituted versions gave novel furo[3,2-d]pyrrolo[1,2-a]azepine products. Such heterocyclic systems would be expected to be useful scaffolds for the preparation of libraries of novel compounds for new drug discovery programs.

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Synthesis of Bridged Heterocycles via Sequential 1,4- and 1,2-Addition Reactions to α,β-Unsaturated *N*-acyliminium Ions: Mechanistic and Computational Studies

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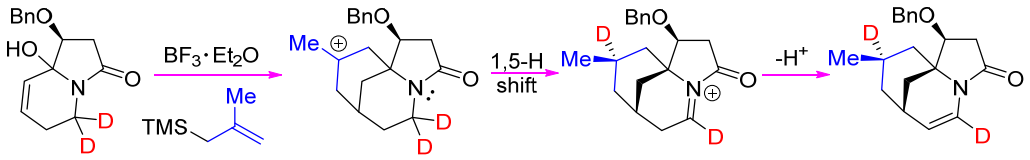
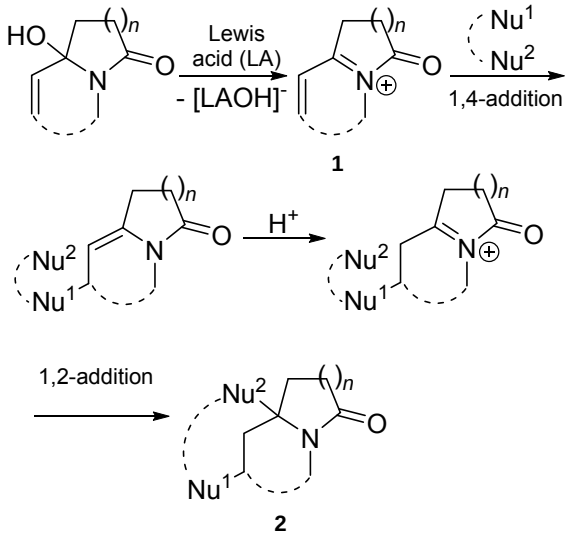


ABSTRACT: Novel tricyclic bridged heterocyclic systems can be readily prepared from sequential 1,4- and 1,2-addition reactions of allyl and 3-substituted allylsilanes to indolizidine and quinolizidine α,β-unsaturated *N*-acyliminium ions. These reactions involve a novel N-assisted, transannular 1,5-hydride shift. Such a mechanism was supported by examining the reaction of a di-deuterated indolizidine, α,β-unsaturated *N*-acyliminium ion precursor which provided specifically di-deuterated tricyclic bridged heterocyclic products and from computational studies. In contrast, the corresponding pyrrolo[1,2-*a*]azepine system did not provide the corresponding tricyclic bridged heterocyclic product and gave only a bis-allyl adduct, while more substituted versions gave novel furo[3,2-*d*]pyrrolo[1,2-*a*]azepine products. Such heterocyclic systems would be expected to be useful scaffolds for the preparation of libraries of novel compounds for new drug discovery programs.

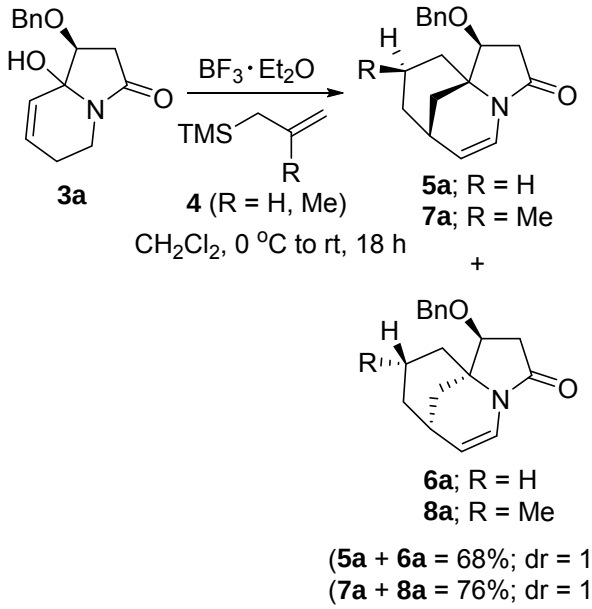
INTRODUCTION

N-acyliminium ions are well recognized as important reactive intermediates in C-C and C-heteroatom bond forming reactions.[1] Both intramolecular[1a–c,d,g] and intermolecular[1a,b,e,f] variants have been extensively developed, with the aforementioned versions providing synthetic access to novel polycyclic, spirocyclic and bridged heterocyclic ring structures. In stark contrast, the chemistry of α,β-unsaturated *N*-acyliminium ions (e.g. **1** in Scheme 1) has been largely undeveloped.[2–4] In principle, these are attractive reactive intermediates for the one-pot synthesis of novel di-functionalized heterocycles (e.g. **2**, Scheme 1) because of their potential for sequential 1,4- and 1,2-addition reactions with two nucleophiles (Nu^1 and Nu^2) under acidic conditions. Significantly, when these two nucleophiles are tethered, or form part of a latent bis-nucleophile, then novel spirocyclic and bridged heterocycles **2** should be realized. These types of molecular architectures are common in bioactive natural products[4] and therefore such a synthetic strategy would be expected to provide structurally diverse scaffolds for new drug discovery and natural product synthesis programs. In an earlier communication we reported the realization of this process for preparing a number of structurally different spirocyclic compounds.[5] We also provided two examples of the synthesis of bridged heterocycles through the preparation of the novel compounds **5a**-**8a** from the BF_3•Et_2O induced reactions of **3a** with allyl- and methallyl-trimethylsilane **4** (R = H and Me, respectively) (Scheme 2).[6] We proposed that these bridged products were formed via a mechanism that involves a transannular 1,5-hydride shift of a carbocation intermediate. We report here a more extensive study of the scope of these reactions, including a mechanistic study employing a di-deuterated analogue of **3a** and a computational study of the key steps of these reaction sequences.

Scheme 1. Proposed reactivity of α,β-unsaturated *N*-acyliminium ions 1.



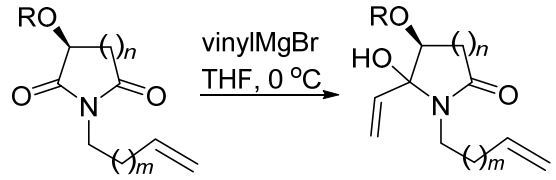
Scheme 2. Synthesis of the novel bridged heterocycles 5-8.



RESULTS AND DISCUSSION

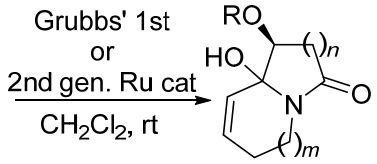
Synthesis of N-acyliminium ion precursors. The bicyclic *N*-acyliminium ion precursors **3a-f,** and **13-15**, required for this study, were prepared according to Schemes 3 and 4, respectively. The pyrrolidinone compounds **9a**, **9b** and **9d** (n = 1) (Scheme 3) were prepared from L-malic acid, while the piperidinone **9d** (n = 2) was prepared from (*S*)-pyroglutamate as described earlier.[5] Compounds **9a-d** were then treated with vinylmagnesium bromide to give the tertiary alcohols **10a-d** (the reaction of **9b** resulted in cleavage of the acetate group giving diol **10b**). Ring closing-metathesis reactions of **10a-d** gave the bicyclic *N*-acyliminium ion precursors **3a-d** in good to high yields. The tertiary alcohols **3e** and **3f** were obtained from **3b** by *O*-tri-isopropylsilylation (TIPSOTf, 2,6-lutidine[7]) or acetylation (Ac_2O, pyridine) (Scheme 3). These compounds were sensitive to degradation and were best prepared just before further chemical reactions.

Scheme 3. Synthesis of *N*-acyliminium ion precursors 3a-f.

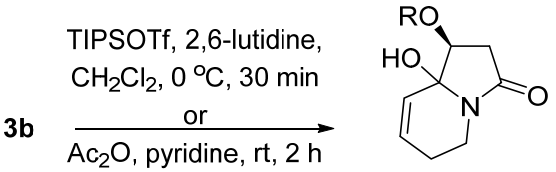


9a, m = n = 1, R = Bn
9b, m = n = 1, R = Ac
9c, m = 1, n = 2, R = Bn
9d, m = 2, n = 1, R = Bn

10a: 76%, m = n = 1, R = Bn
10b: 62%, m = n = 1, R = H
10c: 56%, m = 1, n = 2, R = Bn
10d: 89%, m = 2, n = 1, R = Bn



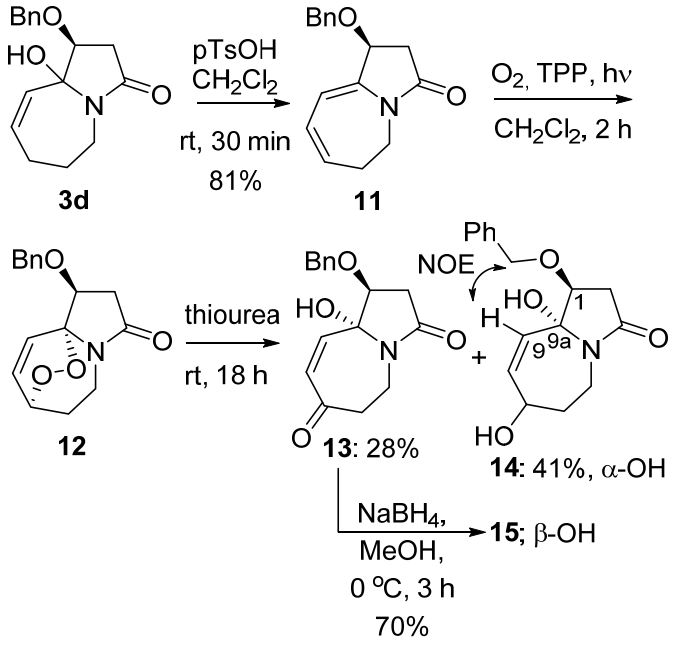
3a: 87%, m = n = 1, R = Bn
3b: 70%, m = n = 1, R = H
3c: 68%, m = 1, n = 2, R = Bn
3d: 89%, m = 2, n = 1, R = Bn



3e: 80%, R = TIPS
3f: 84%, R = Ac

Treatment of **3d** with *p*-toluenesulfonic acid in CH_2Cl_2 at rt for 30 min gave the diene **11** in 81% yield (Scheme 4) which was converted to the *endo*-peroxide **12** upon treatment with singlet oxygen (O_2, meso-tetraphenylporphyrin (TPP), UV light).[8] The stereochemistry of this compound was deduced from the stereochemistry of its related derivatives **14** (Scheme 4) and **33** (Scheme 6) which were established by NOE experiments. Compound **12** was converted to a chromatographically separable mixture of the enone **13** (28% yield) and the α-diol **14** (41% yield) on treatment with thiourea.[8a,9] The configuration at C-9a of **14** was evident from the NOESY correlation between the resonance for H-9 (δ 6.24, (1H, d, J = 12.0 Hz) and one benzyl methylene resonance at δ 4.70 (1H, d, J = 12.0 Hz). Reduction of enone **13** with $NaBH_4$/MeOH stereoselectively gave the β-alcohol **15**.

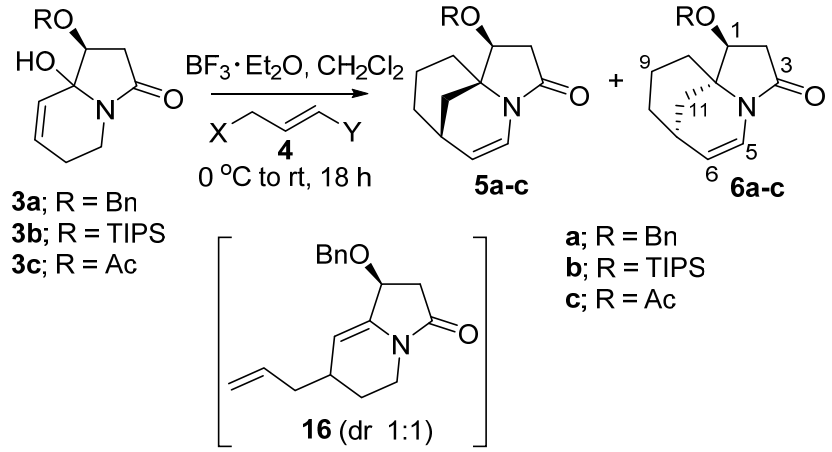
Scheme 4. Synthesis of *N*-acyliminium ion precursors 13-15.



Reactions of α,β-unsaturated *N*-acyliminium ions with allylsilanes. In our first set of experiments, the bicyclic α,β-unsaturated *N*-acyliminium ion precursor **3a** was treated with allyltrimethylsilane **4** (X = TMS, Y = H) (1.2 equiv.) in the presence of BF_3•Et_2O (2 equiv.) in CH_2Cl_2 solution at 0 °C (Table 1). After a short reaction time (1 h) the adduct **16** could be isolated in 68% yield as a 1:1 mixture of chromatographically separable diastereomers. Retreatment of the individual diastereomers of **16** to the above reaction conditions at 0 °C for 1 h and then at rt for 18 h gave the tricyclic bridged compounds **5a** (57% yield) and **6a** (63% yield), respectively. Alternatively, treatment of **3a** with allyltrimethylsilane/BF_3•Et_2O, initially at 0 °C for 1 h and then at rt for 18 h, gave (+)-**5a** and (-)-**6b** as a 1:1 mixture of chromatographically separable diastereomers in 68% yield (Table 1, entry 1). The identity of these compounds was established by 1D and 2D NMR spectroscopic analysis. The unexpected position of the alkene group at C-5−C-6 in **5a** and **6a** was evident from the multiplicities and the relative deshielded and shielded chemical shifts of H-5 (**5a**: δ 7.04 (d, *J* = 8.0 Hz); **6a**: δ 7.03 (d, *J* = 7.0 Hz) and H-6 (**5a**: δ 5.06 (apparent t, *J* = 8.0 Hz); **6a**: δ 5.06

(apparent t, J = 7.0 Hz), respectively, and the 3-bond correlation between H-5 and the carbonyl carbon C-3 in the HMBC spectra of both compounds. The configuration of **6a** was established by NOESY experiments which showed a significant correlation between H-1 (δ 3.81, (1H, apparent t, J = 9.0 Hz)) and one of the methylene bridging protons (H-11β) (δ 1.43 (1H, d, J = 12.0 Hz)) at C-11. With the aim of improving the diastereoselectivities of these reactions, other R substituents on the substrate **3** and other allyl nucleophiles were examined. When the R substituent was changed from Bn to the more hindered TIPS group (**3b**), the yield was improved (78%) however the diastereoselectivity remained unchanged (Table 1, entry 2). The acetate derivative **3c** (R = Ac) also offered no improvement in diastereoselectivity (Table 1, entry 3). This lack of diastereoselectivity was most likely due to the remoteness of the stereogenic center (C-1) in precursors **3a**-**c** to the site of the first addition. In contrast, the reactions of **3a** with the more hindered allylsilane reagents, allyltri*iso*-propylsilane (allylTIPS; **4** (X = TIPS, Y = H)) and allyl*tert*-butyldiphenylsilane (allylTBDPS), were more diastereoselective (dr 30:70, Table 1, entries 4 and 5). In these cases **6a** was favoured over **5a**. The most hindered allyl nucleophile examined, the pinacol boronate, 4,4,5,5-tetramethyl-2-[(1*E*)-3-[tris(1-methylethyl)silyl]-1-propen-1-yl]-1,3,2-dioxaborolane,[10] however, showed no diastereoselectivity (Table 1, entry 8). When some of these reactions were initiated at -78 ^{o}C, and then warmed slowly to rt, no improvement in diastereoselectivities were observed. Allyltributylstanne only produced the initial adduct **16** (72%, dr 1:1, Table 1, entry 9).

Table 1. Synthesis of bridged tricyclics 5a-c and 6a-c

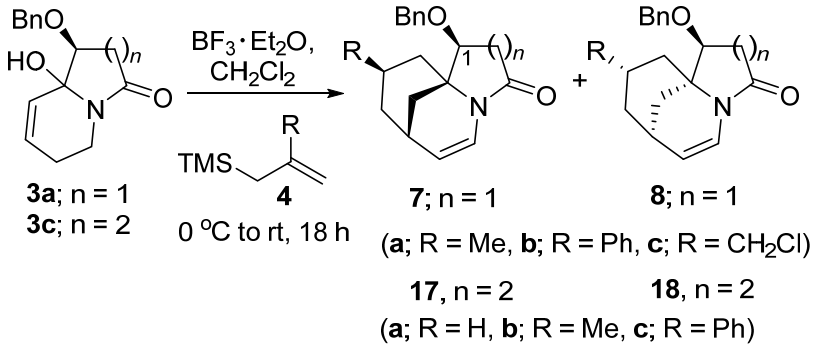


Entry	R of **3**	X, Y of **4**	Yield (%)[a]	Diastereoselectivity (**5**:**6**)[b]
1	Bn	TMS, H	68	1:1
2	TIPS	TMS, H	78	1:1
3	Ac	TMS, H	70	1:1
4	Bn	TIPS, H	75	30:70
5	Bn	TBDPS, H	62	30:70
6	Bn	PinB, H	71	1:1
7	Bn	KF_3B, H	53	1:1
8	TIPS	TIPS, PinB	71	1:1
9	Bn	Bu_3Sn, H	72 (**16**)	1:1

[a]Combined yield of **5** and **6** after column chromatography. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. Pin = pinacol.

We next examined the scope of these reactions towards 2-substituted allyltrimethylsilanes (Table 2). Under the standard conditions the reaction of **3a** with methallyltrimethylsilane (**4**; R = Me)/BF_3•Et_2O gave (+)-**7a** (R = Me) and (-)-**8a** (R = Me), respectively, as a 1:1 mixture of chromatographically separable diastereomers (Table 2, entry 1).

Table 2. Synthesis of bridged tricyclics 7a-c, 8a-c, 17a-c and 18a-c.



Entry	n	R	Yield of **7** and **8** or **17** and **18** (%)[a]	Diastereoselectivity[b] **7:8** or **17:18**
1	1	Me	76	1:1
2	1	Ph	61 + **19** (5%)	70:30
3	1	CH_2Cl	72	1:1
4	2	H	85	1:1
5	2	Me	83	1:1
6	2	Ph	58	70:30

[a]Combined yield of **7** and **8** or **17** and **18** after column chromatography. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture.

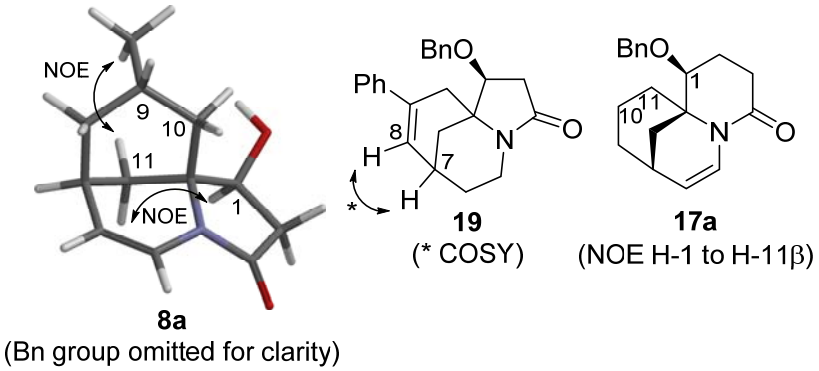


Figure 1. ^{1}H NMR correlations for compounds **8a**, **17a** and **19**.

The configuration of the methyl bearing methine group (C-9) in **8a** was established as *exo* with respect to the methylene bridge from 1D NOE difference experiments (Figure 1). A significant NOE was observed between H-1 (δ 3.81 (1H, apparent t, J = 9.0 Hz)) and one of the bridging methylene protons (H-11α) (δ 1.42, (1H, d, J = 8.0 Hz)) at C-11 and between the C-9 methyl group (δ 0.92, (1H, d, J = 6.0 Hz)) and the other bridging methylene proton (H-11β) (δ 1.95, (1H, d, J = 8.0 Hz)) at C-11. In contrast, the reaction of **3a** with 2-phenylallyltrimethylsilane[11]/BF_3•Et_2O gave not only the bridged products **7b** (R = Ph) and **8b** (R = Ph), as a 70:30 mixture of chromagraphically separable diastereomers, but a small amount (5% isolated yield) of the bridged compound **19** (single diastereomer, Figure 1) in which the double bond was in the ring arising from the allylsilane component (Table 2, entry 2). The position of the double bond in **19** was evident from the COSY correlation between H-7 and H-8 (Figure 1). The analogous reaction of 2-chloromethylallyltrimethylsilane with **3a** gave **7c** (R = CH_2Cl) and **8c** (R = CH_2Cl), respectively, as a 1:1 mixture of separable diastereomers (Table 2, entry 3).

Notably, compounds **6a-c** and **8a-b** with the methylene bridge between C-7 and C-10a or C-8 and C-11a, respectively, having the α-configuration showed small and negative specific optical rotations and in the ^{1}H NMR spectrum H-1 resonated as a doublet of 5.0 Hz. While compounds **5a-c** and **7a-b**, with the methylene bridge having the β-configuration, showed a relatively larger positive specific optical rotation and in the ^{1}H NMR spectrum H-1 resonated as an apparent triplet of 9.0 Hz. The Ph-substituted derivative **8c**, however, had a relatively large positive specific optical rotation and in the ^{1}H NMR spectrum H-1 resonated as a doublet of 5.0 Hz. Although we could not obtain unequivocal NOESY or ROESY NMR evidence for the configuration of this compound we tentatively assigned its structure by

analogy with **6a-c** and **8a-b** based on the multiplicity of H-1 (δ 3.81, (1H, d, *J* = 5.0 Hz)) in its ^{1}H NMR spectrum.

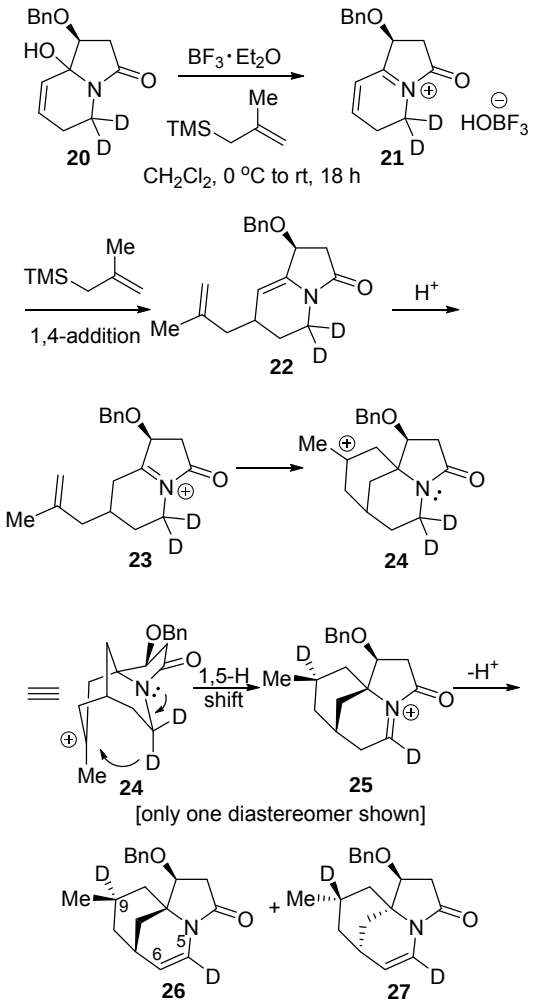
The bridged heterocycles **17** and **18**, based on a homologous quinolizinone skeleton, were readily obtained from the reactions of the quinolizinone derived α,β-unsaturated *N*-acyliminium ion precursor **3c** with allyltrimethylsilanes **4** (R = H, Me, Ph)/BF_3•Et_2O (Table 2, entries 4-6). For the allyltrimethylsilanes (R = H and Me) the yields of bridged products **17a,b** and **18a,b** were higher than those for **5a,b** and **6a,b** from **3a**, while the reaction between 2-phenylallyltrimethylsilane, BF_3•Et_2O and **3c** gave a 70:30 diastereomeric mixture of chromatographically separable bridged tricycles **17c** and **18c** (R = Ph), respectively. None of the product corresponding to the homologue of **19** could be isolated.

The structure of (-)-**17a** was evident from the NOESY correlation between H-1 (δ 3.40, (1H, s)) and one of the C-11 methylene protons (H-11β) (δ 1.36 (1H, d, *J* = 11.0 Hz)) (Figure 1). While its diastereomer (+)-1**8a** had a specific rotation of opposite sign and H-1 resonated at δ 3.38 as a doublet of doublets (*J* = 4.6, 12.0 Hz)). The same trend in specific rotation and the multiplicity of the H-1 resonance was found in the diastereomeric pairs of compounds **17b/18b** and **17c/18c**.

Deuterium labeling studies. To support our initially proposed mechanism to explain the formation of the bridged products **5-8**, the di-deuterated analogue **20** (Scheme 5) of the *N*-acyl iminium ion precursor **3a** was prepared via the corresponding di-deuterated analogues of **9a** and **10a**. The former derivative was prepared from the condensation reaction between but-3-en-1,1-d_2-1-amine[12] and L-malic acid (see the Experimental section for details). Treatment of **20** with methallyltrimethylsilane/BF_3•Et_2O gave the specifically labeled di-deuterated bridged products **26** and **27** in 75% yield as a 1:1 mixture of diastereomers (Scheme 5). These could be separated by further column chromatography. The positions of the deuterium labels

in these compounds were clearly apparent from ^{1}H and ^{13}C NMR spectroscopic analysis. For example, in the ^{1}H NMR spectrum of **26**, the resonance associated with the methyl substituent was now observed as a singlet at δ 0.84 (3H). While the resonance associated with the most deshielded enamide proton at H-5 in **7a** was completely absent and the multiplicity of the other enamide proton (H-6) had changed from a doublet of doublets in **7a** (R = Me) to a doublet resonance (δ 5.10, J = 6.0 Hz)) in the ^{1}H NMR spectrum of **26**. Further, in the ^{13}C NMR spectrum of **26**, resonances associated with the enamide carbon C-5 (δ 123.0 (t, $J_{C\text{-}D}$ = 26.8 Hz)) and the methine carbon C-9 (δ 24.5 (t, $J_{C\text{-}D}$ = 19.3 Hz)) showed $J_{C\text{-}D}$ coupling.

Scheme 5. Deuterium labeling studies on 20



Related differences in the NMR spectra of **27** when compared to those of **8a** were also observed.

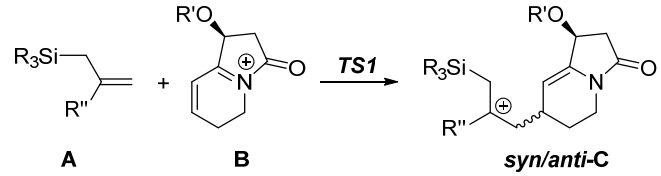
These labeling studies support the mechanism outlined in Scheme 5. The reaction of **20** with BF_3•Et_2O gives the α,β-unsaturated *N*-acyliminium ion intermediate **21** which undergoes a 1,4-addition reaction with the allylsilane reagent to give the initial adduct **22** (Scheme 5). This compound then undergoes protonation (by $HOBF_3^-$ or its derivative) to generate the N-acyliminium ion **23** which upon an intramolecular cyclization reaction (1,2-addition reaction) gives the tricyclic carbocation intermediate **24**. This intermediate undergoes a transannular 1,5-hydride shift to give the *N*-stabilized carbocation intermediate **25**, and its diastereomer, which then give the enamides **26**/**27** upon loss of a proton. Such transannular 1,5-hydride shifts have precedent.[13] Cases involving *N*-stabilization however, are rare. In the case of the reaction of **3a** with 2-phenylallyltrimethylsilane/BF_3•Et_2O a small amount of the tricyclic compound **19** was also isolated, resulting from elimination of a proton from the non-deuterated, phenyl analogue of intermediate **24**. In this intermediate, the Ph substituent stabilizes the carbocation such that the 1,5-hydride transfer mechanism is relatively slower allowing a small amount of the 1,2-elimination product (**19**) to form.

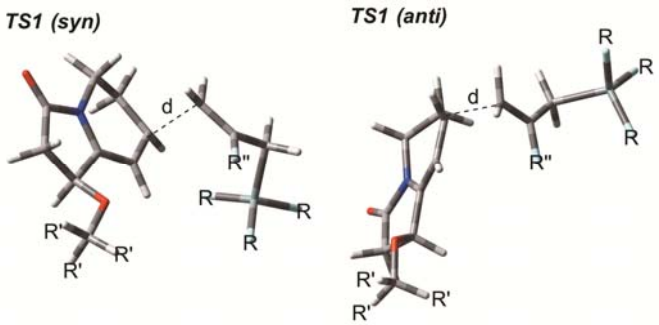
Computational studies. In order to explore the mechanism of this sequence in more detail, the key reaction steps, e.g. (i) the allylsilylane addition to the α,β-unsaturated *N*-acyliminium ion precursor, and (ii) the subsequent nucleophilic cyclization/1,5-hydride shift were studied with computational methods. Geometry optimizations and frequency analyses for all ground and transition state structures were performed using the B3LYP[14] and M06-2X[15] density functional methods, in combination with the 6-31G* and 6-31+G* basis sets[16] using the Gaussian09 software package.[17] Selected reactions were also computed with the M06-2X/6-31+G* method using the D3 version of Grimme's dispersion with the original D3 damping function.[18] Calculations in dichloromethane were performed for selected reactions using the

Conductor-like Polarizable Continuum Model (CPCM).[19] All ground and transition states were verified by vibrational frequency analysis at the same level of theory, and all identified transition states showed only one imaginary frequency.

To gain insight into the diastereoselectivity of the allylation step, we explored the addition from the same (*syn*) and opposite side (*anti*) of the pyrrolidinone ring substituent (OR' in **B**). The results are compiled in Table 3 for various model allylsilanes **A** and α,β–unsaturated *N*-acyliminium ions **B**.

Table 3. Addition of allylsilanes A to α,β-unsaturated *N*-acyliminium ions B: Calculated potential energy surface and distance (d) between reaction centers in transition state *TS1* (free energies in kJ mol^{-1}).[a]





Entry	R	R'	R″	*TS1*	d / Å	C
1[b]	H	Me	H	83.2	1.924	81.2 (*syn*)
2[c]	H	Me	H	69.0	2.027	47.0 (*syn*)[d]
3[e]	H	Me	H	88.8	2.110	37.3 (*syn*)[d]
4[f]	H	Me	H	72.0[g]	2.025	44.4 (*syn*)[d]

5[h]	H	Me	H	86.2	2.110	34.9 (*syn*)[d]
6[b]	H	Me	H	99.8	1.974	86.1 (*anti*)
7[c]	H	Me	H	89.5	2.058	53.2 (*anti*)[d]
8[e]	H	Me	H	100.0	2.126	37.5 (*anti*)[d]
9[f]	H	Me	H	87.2	2.056	50.6 (*anti*)[d]
10[h]	H	Me	H	97.6	2.124	35.0 (*anti*)[d]
11[b]	H	Bn	H	78.8	1.913	85.6 (*syn*)
12[b]	H	Bn	H	104.1	1.962	91.6 (*anti*)
13[b]	iPr	Me	H	56.1	2.124	23.4 (*syn*)[d]
14[b]	iPr	Me	H	62.7	2.120	22.7 (*anti*)[d]
15[b]	iPr	Bn	H	63.6	2.126	30.1 (*syn*)[d]
16[b]	iPr	Bn	H	68.5	2.105	29.7 (*anti*)[d]
17[b]	H	Me	Ph	41.7	2.313	7.7 (*syn*)
18[b]	H	Me	Ph	49.4	2.236	8.1 (*anti*)
19[b]	Me	Me	Ph	37.4	2.394	-12.1 (*syn*)
20[c]	Me	Me	Ph	--[i]	--	-38.5 (*syn*)
21[e]	Me	Me	Ph	--[i]	--	-29.7 (*syn*)
22[b]	Me	Me	Ph	35.9	2.195	-20.0 (*anti*)
23[c]	Me	Me	Ph	17.6	2.154	-48.4 (*anti*)[d]
24[e]	Me	Me	Ph	30.9	2.183	-46.1 (*anti*)[d]

[a]ΔG values are relative to compound reactants **A** and **B**. [b]B3LYP/6-31G*. [c]M06-2X/6-31+G*. [d]Elongated C–Si bond (see text). [e]M06-2X/6-31+G* in dichloromethane. [f]M06-2X/6-31+G* with D3 dispersion. [g]Transition state associated with two negative vibrations (see text).

[h]M06-2X/6-31+G* with D3 dispersion in dichloromethane. [i]Transition state could not be located (see text).

According to the computational predictions, the reaction likely occurs through initial formation of a reactant complex, which is *ca* 20 kJ mol^{-1} higher in energy than the free reactants (data not shown). Comparison of the data in entries 1-5 and 6-10 show some variation of the data with the level of theory. Thus, the gas phase computations using the M06-2X/6-31+G* method, which has been shown to address standard non-covalent interactions with reasonable accuracy,[20] predict ***TS1*** about 10-15 kJ mol^{-1} below the values obtained with B3LYP/6-31G*, which, on the other hand, computes energies for ***TS1*** similar to M06-2X/6-31+G* in dichloromethane. Inclusion of the D3 dispersion correction in the M06-2X calculations does not lead to significantly different energies (entries 4, 5 and 9, 10). However, it should be noted that ***TS1*** in entry 4 is characterised by two negative frequencies. Thus, the vibrational mode associated with the addition (-345.3 cm^{-1}) is accompanied by a very weak negative vibration (-2.7 cm^{-1}) that corresponds to a rocking motion of the two molecular fragments and which cannot be eliminated. The considerably lower energy of product **C** (and therefore lower endothermicity of the addition process) predicted by M06-2X for both gas phase and in dichloromethane could be due to a slightly different geometry of **C** that is characterised by a considerably elongated C-SiH_3 bond (2.05 – 2.09 Å) and shortened C–C bond (1.38 Å), compared to B3LYP (C-SiH_3: 2.02 Å; 'C-C': 1.41 Å). Overall, except for the reaction system in entries 19-24 (see below), all of these methods predict that both *syn* and *anti* addition are energetically very similar with the *syn* pathway being slightly more favourable by a few kJ mol^{-1}.

A considerable influence of the substitution pattern in allylsilane **A** on the energy profile of the addition process is apparent. Thus, increasing the electron density at Si by replacing H

with alkyl substituents lowers the transition state for the addition, ***TS1***, and renders the reaction energetically more favourable. This can be rationalized by the β-silicon effect, which stabilizes cations β to the Si atom through hyperconjugation.[21] In fact, the optimized structures for **C** with R = *i*Pr indicate an advanced dissociation into $i\text{Pr}_3\text{Si}^+$ and the corresponding alkene (C–SiR_3 distance = 2.15 Å), e.g. formation of the product of type **16** (see Table 2). Additional stabilization of the positive charge in **C**, e.g. when R" = Ph (entries 17-24), further lowers the energy of both ***TS1*** and **C**.

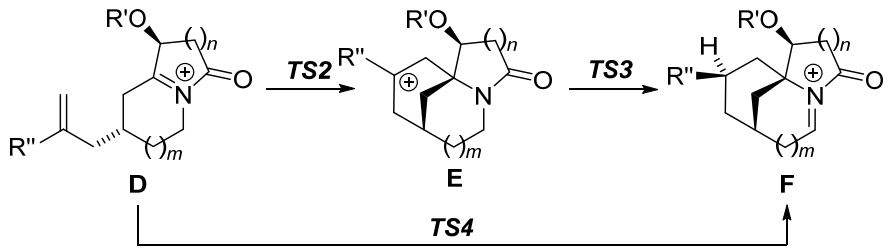
Analysis of the ***TS1*** geometry reveals that, irrespective of the theoretical level, in systems with low steric hindrance the distance (d) between the reaction centers for the *syn* addition is slightly shorter than for the *anti* attack. It is apparent that steric effects due to the 'remote' substituents R on the allylsilane and R' at the stereocenter in **B** are too small to induce considerable face discrimination in ***TS1***. The system has sufficient conformational flexibility that, even when R' = Bn, addition of the allylsilane could occur in both *syn* and *anti* fashion in such way that steric hindrance can be largely avoided. This is further supported by the energies of adduct **C**, which are very similar for the *syn* and *anti* addition when R" = H. Interestingly, increasing the size of the substituent R" from H to Ph results in a considerably elongated distance between the reaction centers by 0.1-0.2 Å for the *syn* addition and also a slight elongation for the *anti* attack, which is indicative for an earlier transition state. This corresponds well with the computed lower barrier for the reactions involving the 2-phenyl substituted allylsilanes and the stronger exothermicity of these reactions, in accordance with the Hammond postulate.[22]

According to the B3LYP computations, ***TS1*** for *syn* and *anti* addition addition of **A** to **B** for R = R' = Me and R" = Ph are very similar, indicating a non-diastereoselective reaction (entry 19 vs. 22). The M06-2X method reveals the same trend on ***TS1*** for both for gas phase and in

dichloromethane for the *anti* attack as for the other systems studied in this work. However, it is worth noting that ***TS1*** for the *syn* addition could not be located with M06-2X (entries 20 and 21). The experimentally observed formation of **7b** as the major diastereomer that is formed through *anti* allylation of **3a** (Table 2, entry 2) can be rationalised by the stability of the corresponding adduct **C**. Thus, irrespective of the level of theory, the calculations predict *syn*-**C** as an 'intact' molecule with a covalent C–Si bond (C–$SiMe_3$ distance ca. 2.02 Å). In contrast to this, the M06-2X calculations reveal a clearly elongated C–Si bond in the corresponding *anti*-**C** (C–$SiMe_3$ distance ca. 2.06 Å), indicating partial dissociation into the final alkene of type **16**. We believe that formation of *syn*-**C** is reversible, and equilibration leads ultimately to the thermodynamically more stable *anti*-**C**. In contrast to this, in the case of less stabilized adducts **C** the subsequent desilylation through C–Si bond cleavage should be faster than reverse fragmentation into **A** and **B**, so that a kinetically controlled product distribution is obtained.

We next explored the energy profile for the subsequent nucleophilic cyclization/1,5-hydride shift. The calculated data for the model system **D** → **E** → **F** are shown in Table 4.

Table 4. Calculated potential energy surface for the nucleophilic cyclization/1,5-hydride shift D → E → F (free energies in kJ mol^{-1}).[a,b]



Entry	R'	R″	*m,n*	***TS2***	**E**	***TS3***	**F**	***TS4***
1[c]	Me	H	1,1	--[d]	--[d]	--[d]	-65.0	70.4

2[e]	Me	H	1,1	--[d]	--[d]	--[d]	-91.2	63.6
3[f]	Me	H	1,1	--[d]	--[d]	--[d]	-84.8	54.0
[4[c]	Me	H	1,1	--[d]	--[d]	--[d]	-22.2	74.4][g]
5[c]	Me	Me	1,1	53.1	43.3	45.9	-53.5	
6[e]	Me	Me	1,1	42.6	28.7	29.3	-82.6	
7[f]	Me	Me	1,1	42.1	3.4	19.7	-76.5	
[8[c]	Me	Me	1,1	57.2	42.6	48.9	2.7][g]	
[9[e]	Me	Me	1,1	44.9	27.0	32.4	-21.5][g]	
[10[f]	Me	Me	1,1	50.5	11.5	27.0	-19.3][g]	
11[c]	Me	Ph	1,1	28.5	-6.3	24.1	-51.7	
12[e]	Me	Ph	1,1	18.4	-8.8	12.1	-81.6	
13[f]	Me	Ph	1,1	31.9	-11.9	19.0	-76.7	
[14[c]	Me	Ph	1,1	42.7	2.2	39.3	14.9][g]	
[15[e]	Me	Ph	1,1	35.2	-2.6	25.8	-15.1][g]	
[16[f]	Me	Ph	1,1	51.0	-0.1	36.3	-13.5][g]	
17[c]	Me	CH_2Cl	1,1	87.4	79.3	81.0	-39.9	
[18[c]	Me	CH_2Cl	1,1	77.4	67.9	69.9	3.3][g]	
19[c]	Bn	Me	1,1	55.0	41.8	46.4	-54.0	
[20[c]	Me	Me	1,2	89.2	85.8	--[c]	13.8][g]	
[21[h]	Me	Me	1,2	76.7	70.8	--[d]	-17.0][g]	
22[c]	Me	Me	2,1	55.8	53.6	--[d]	-33.4	

[a]ΔG vaiues are relative to compound **D**. [b]Scheme shows formation of the β-configuration at the methylene bridge, which results from cyclization of the *anti* isomer. [c]B3LYP/6-31G*. [d]Could not be located. [e]M06-2X/6-31+G*. [f]M06-2X/6-31+G* in dichloromethane. [g]Data in

square brackets are for cyclization of the *syn* isomer that leads to the α-configuration at the methylene bridge. [h]M06-2X/6-31G*.

When **D** has a non-branched propene substituent (R" = H), the computations predict a one-step process via ***TS4*** for the rearrangement (entries 1 – 4). A stable ground state structure of the cationic intermediate **E** could not be located with neither the B3LYP/6-31G* (entries 1 and 4) nor the M06-2X/6-31+G* method for both gas phase (entry 2) and in dichloromethane (entry 3), respectively. The concerted nature of the cyclization/rearrangement **D** → **F** was confirmed through intrinsic reaction coordinate calculations (IRC) at the B3LYP/6-31G* level. When R" ≠ H the stability of **E** increases, and ground state structures could be located. The gas phase calculations predict for R" = alkyl that formation of the intermediate **E** is an endothermic process. This is plausible, since the resonance stabilization of the positive charge in carbocation **D** is lost upon cyclization to **E**. However, as shown by the exemplary calculations for **D** with R" = Me, the intermediate **E** experiences a considerable stabilization in dichloromethane (entries 7 vs. 5, 6 and 10 vs. 8, 9). Thus, cyclization of *anti*-**D** (with R' = R" = Me) to **E** becomes a practically energy neutral process (entry 7), whereas the corresponding cyclization of *syn*-**D** is slightly more endothermic (entry 10). In fact, a stabilizing effect of the solvent is apparent throughout the sequence **D** → **F**, which leads not only to lower energies for ***TS2*** and ***TS3*** in general, but also to a significant stabilization of all ground states, compared to the gas phase. This has implications for the rearrangement **E** → **F** though ***TS3***, where the gas phase calculations predict a rapid process through a very low barrier, whereas in dichloromethane this process is slower. It is, however, important to point out that, irrespective of the theoretical method, the sequence *anti*-**D** → β-**F** is kinetically and thermodynamically more preferred than *syn*-**D** → α-**F**. Further, it is reasonable to assume that

the subsequent deprotonation of **F** to yield stable products of type **5-8** will be very fast, providing ultimately the thermodynamic driving force for the overall sequence.

In the case of R" = Ph cyclization of **D** leads to the resonance stabilized intermediate **E** in an exothermic reaction (entries 11-16). Rearrangement of the latter to **F** through hydride migration is also exothermic, but associated with a considerable activation barrier (***TS2***). Because of this, competing reactions can occur, for example deprotonation, which explains formation of by-product **20** in the reaction of **3a** with **4** (R = Ph, see Table 2). However, contrary to the system with R' = alkyl described above, the influence of solvent on ***TS2***, ***TS3*** and **E** is less pronounced. Exploration of the reason for the different outcome clearly requires further investigations, which are beyond the scope of the present study. However, in general the M06-2X/6-31+G* calculations for both gas phase and in dichlormethane predict formation of **F** being about 20-30 kJ mol^{-1} more exothermic than the gas phase B3LYP/6-31G* method.

The computed higher energies for ***TS2***, **D** and ***TS3*** in the case of R" = CH_2Cl (entries 17, 18) can be attributed to the fact that the cyclization/rearrangement process involves development of an energetically unfavourable positive charge α to the electron-withdrawing chloromethyl substituent.

Similar to the addition of allylsilane **A** to *N*-acyliminium ion **B**, the substituent R' in the pyrrolidinone does not influence the reaction outcome (entry 19 vs. 5). Inspection of the geometries of **D**, **E** and ***TS2*** (not shown) reveals that even the large OBn substituent has sufficient conformational flexibility to avoid steric interactions with the allyl side chain.

Evaluation of the experimental findings and the computational predictions presented in Tables 3 and 4 clearly indicate that the diastereoselectivity of the entire sequence is determined by the addition of the allylsilane to the α,β-unsaturated *N*-acyliminium ion **B** and

the stability of the intermediate cation **C**. Thus, when R" = H, Me (or CH_2Cl), this addition is largely unselective, leading to a 1:1 mixture of products (**5** + **6** and **7** + **8**, respectively). In the case of R" = Ph, the major product **7** possesses the β-configuration at the methylene bridge (Table 2, entry 2). As mentioned above, this can be rationalised by the preferred formation of the respective *anti*-**C** intermediate, which is further amplified by its faster subsequent rearrangement through nucleophilic cyclization/1,5-hydride transfer (Table 4, entries 11-13 versus 14-16). On the other hand, the preferential formation of **6** possessing the α-configuration at the methylene bridge (Table 1, entries 4 and 5) is less obvious. There seems to be a not yet understood directing effect of the bulky silyl group that supports *syn* addition of the allylsilane, which warrants further investigation.

It should be noted that increasing the size of either of the rings in the α,β-unsaturated *N*-acyliminium ion affects the entire sequence considerably. Thus, according to the computations, the barrier ***TS2*** and the energy of intermediate **E** in the homologous quinolizinone (m = 1, n = 2) are both higher than for the smaller homologue (entry 20 and 21 vs. 8-10). Although a transition state for the 1,5-hydride shift could not be located, the distance between the carbon centres involved in this transfer is significantly larger than in the smaller indolizidinone derived intermediate **E** (3.241 Å vs. 2.268 Å). This indicates that for the hydride transfer to occur in the quinolizinone derived intermediate **E**, considerable conformational changes are required.

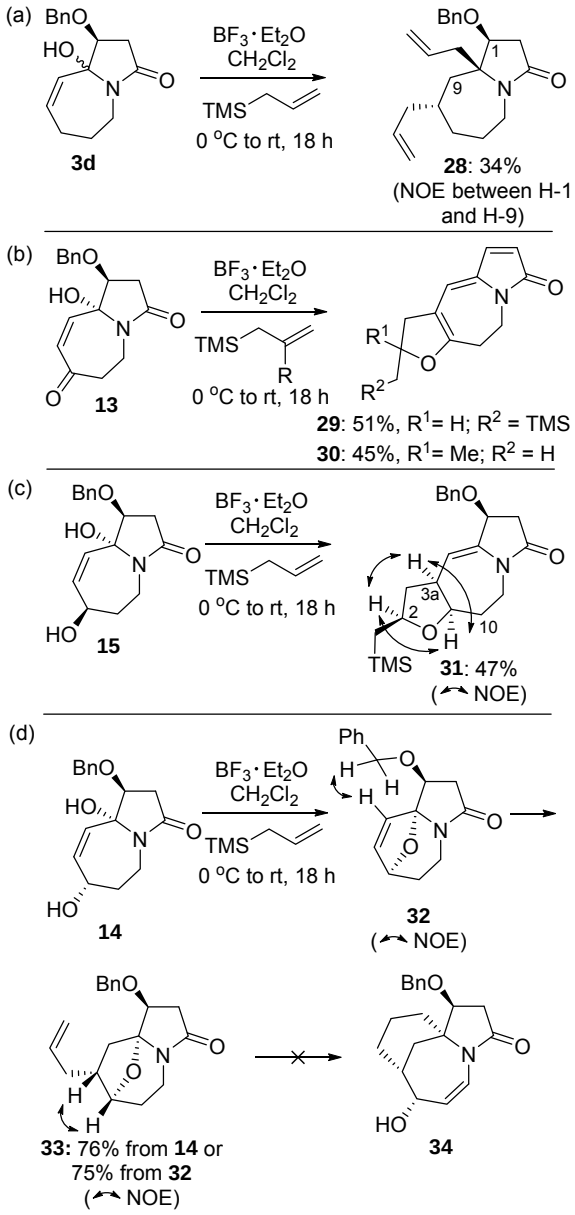
In the case of pyrrolo[1,2-*a*]azepines (**D** with m = 2, n = 1), the B3LYP/6-31G* computations predict that the nucleophilic cyclization should principally occur at a similar rate than in the indolizidines. However, ***TS3*** for the corresponding subsequent transannular hydride shift could not be located (Table 4, entry 22). In fact, inspection of the geometry (not shown) reveals that the 'reactive' conformation would require eclipsed adjacent methylene groups,

which is energetically highly unfavourable. This prediction was confirmed experimentally. Thus in contrast to the chemistry found on the aforementioned indolizidinone (**3a**-**b**) and quinolizinone (**3c**) systems, the pyrrolo[1,2-*a*]azepines **3d** and **13**-**15** also gave some highly unexpected reaction products (Scheme 6).

Reactions of pyrrolo[1,2-*a*]azepines. The reaction of the bicyclic α,β-unsaturated *N*-acyliminium ion precursor **3d** with allyltrimethylsilane (1.2 equiv.)/BF_3•Et_2O gave a low yield (34%) of the bis-allylated product **28** as a single diastereomer (Scheme 6(a)). Other products were formed but could not be isolated in sufficient purities for characterization. The configuration assigned to C-9a in **28** was based on the significant NOE correlation between the resonances for H-1 and H-9β. Our attempts at a ring-closing metathesis reaction of **28** with Grubbs' first or second generation Ru catalysts (CH_2Cl_2, rt to reflux or toluene at 80 ^oC) resulted in only recovered starting material, which indicated that the two allyl groups may have an *anti* stereochemical relationship as shown in structure **28**.

The reactions of **13** with allyl- and methallyl-trimethylsilane/BF_3•Et_2O gave the highly conjugated tricyclic trieneones (furo[3,2-*d*]pyrrolo[1,2-*a*]azepines) **29** and **30**, respectively (Scheme 6(b)). In both products elimination of the OBn group had occurred and, surprisingly in **29** the TMS group of the allyltrimethylsilane had been retained, while in **30** this group had been lost to form part of a gem-dimethyl substituent. A possible mechanistic scheme to explain the formation of these products is provided in Scheme 7(a). 1,4-Addition of allyltrimethylsilane to the α,β-unsaturated N-acyliminium ion intermediate formed from **13** would give the cationic intermediate **35**, stabilized by the β-TMS group. This cation is

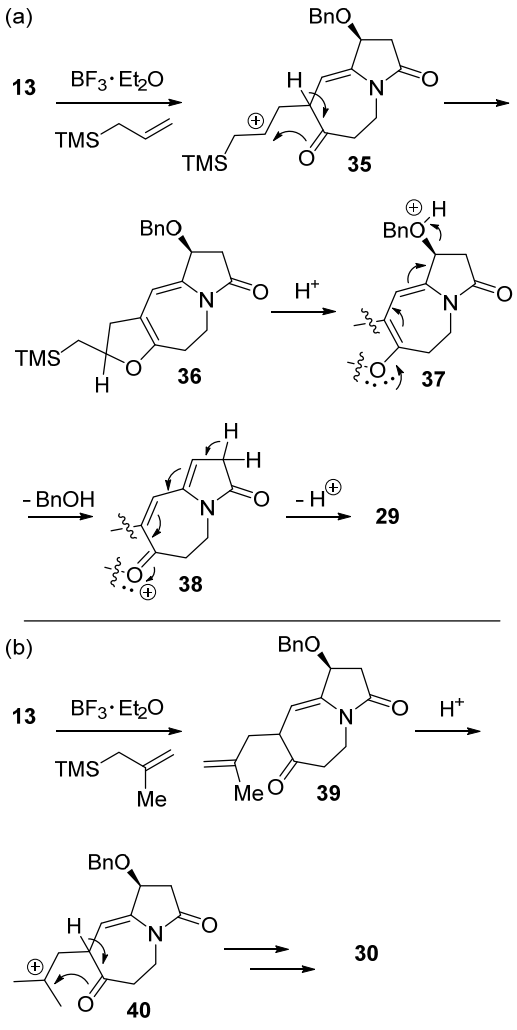
Scheme 6. Reactions of pyrrolo[1,2-*a*]azepines



trapped by the enol form of the proximal ketone group of **35** to give the tetrahydrofuran intermediate **36**. Furan-oxygen assisted elimination of benzyl alcohol from the protonated intermediate **37** followed by loss of a proton would then lead to the observed product **29** with retention of the TMS group. In the case of the reaction of **13** with methallyltrimethylsilane/BF_3•Et_2O the analogous incipient cationic intermediate to **35** is more sterically hindered to attack by the ketone and thus more readily loses the TMS group to give the alkene intermediate **39** (Scheme 7(b)). Protonation of the alkene group then gives the tertiary cation intermediate **40** which can undergo a similar sequence of reaction events as

intermediate **35** to give the observed tricyclic product **30**. The β-alcohol analogue **15** of **13** gave a similar tricyclic product **31** in 47% yield upon reaction with allyltrimethylsilane/BF_3•Et_2O, with retention of the TMS group and the *O*-benzyl substituent. The configuration at C-2, C-3a and C-10a in **31** was evident from NOESY NMR experiments which showed mutual NOE correlations between H-2, H-3a and H-10a (Scheme 6(c)). This seems to be the first report of the synthesis of a furo[3,2-*d*]pyrrolo[1,2-*a*]azepine.

Scheme 7. Proposed mechanisms for the formation of compounds 29 and 30



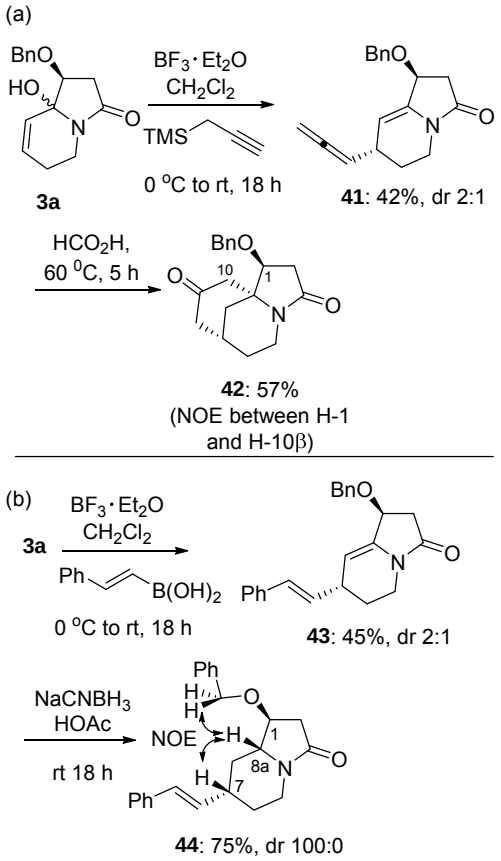
In contrast, the reaction of allyltrimethylsilane with **14** gave the adduct **33** in 76% yield as a single diastereomer (Scheme 6(d)). This product was formed via the tricyclic intermediate **32** which could be isolated in 80% yield after quenching the reaction after a short reaction time

at 0 ^{o}C. Treatment of **32** with allyltrimethylsilane/BF_3•Et_2O at rt gave the allylated product **33** in 75% yield. The stereochemistries of **32** and **33** were established by NOE experiments which showed significant correlations between the resonances for the benzyl protons and the alkene proton H-9 and the vicinal methines shown on structures **32** and **33**, respectively (Scheme 6(d)). Compound **33** could not be induced to cyclize to the bridged compound **34** by further treatment with BF_3•Et_2O or protic acids (TFA, TsOH or formic acid). Only unreacted **33** was recovered from these reactions.

To examine further reactions of the indolizidine **3a** it was treated with propargyltrimethylsilane[23] to give a 2:1 mixture of allene diastereomers **41** (Scheme 8(a)) The major diastereomer cyclized upon exposure to formic acid at 60 ^{o}C[24] to give, after base treatment, the novel bridged tricyclic ketone **42** in 57% yield. The stereochemistry of **42** was assigned from ROESY NMR analysis which showed a correlation between the resonance for H-1 (δ 3.77 (1H, t, J = 6.5 Hz) and the resonance for one of the diastereotopic C-10 protons (H-10β, δ 2.41 (1H, d, J = 17.5 Hz)) (Scheme 8(a)). The "*anti*" stereochemistry of the major diastereomer of **41** is analogous to that of the major diastereomer of the diene **43** formed from the reaction of **3a** with (*E*)-β-styreneboronic acid/BF_3•Et_2O.[25] This major diastereomer underwent a diastereoselective reduction with $NaCNBH_3$/HOAc to give the disubstituted indolizidinone **44** (Scheme 8(b)) in which the configurations at the newly formed stereogenic centers could be assigned from NOE experiments. The NOE correlations between the resonances for H-7 and H-8a indicated these protons had a 1,3-diaxial relationship, while the NOE correlation between the resonances for H-8a and the OBn methylenes indicated that these protons and H-7 were all on the same face of the indolizidinone ring (Scheme 8(b)). Thus the reduction of the *N*-acyl iminium intermediate formed from protonation of the enamide of **43**, in the conversion of **43** to **44**, is a result of the expected axial attack by this

hydride reducing agent from the β-face through a transition state conformation in which the C-1 and C-7 substituents are pseudo-equatorial.[26]

Scheme 8. Synthesis of indolizidinone derivatives 41−44



CONCLUSIONS

In conclusion, novel tricyclic bridged heterocyclic systems can be readily prepared from sequential 1,4- and 1,2-addition reactions of allyl- and 2-substituted-allylsilanes to indolizidine and quinolizidine α,β−unsaturated *N*-acyliminium ions. These reactions involve a novel N-assisted transannular 1,5-hydride shift. Such a mechanism was supported by examining the reaction of a di-deuterated α,β-unsaturated *N*-acyliminium ion precursor which provided specifically di-deuterated tricyclic bridged heterocyclic products and from

computational studies. The latter study indicated that the transannular 1,5-hydride shift proceeds rapidly with a very low or virtually non-existent activation barrier. Overall, according to the computations, the diastereoselectivity of the entire sequence is determined in the allylation of the α,β-unsaturated *N*-acyliminium ion, which leads to the corresponding adducts *syn*/*anti*-**C** in a kinetically controlled fashion. In the case of highly stabilized carbocations, it is proposed that the allylation is reversible and leads ultimately the thermodynamically most stable adduct. In contrast, an α,β-unsaturated *N*-acyliminium ion derived from the corresponding pyrrolo[1,2-*a*]azepine system did not provide the corresponding tricyclic bridged heterocyclic product and gave only a bis-allyl adduct, while more substituted versions gave novel furo[3,2-*d*]pyrrolo[1,2-*a*]azepine products. The reaction of an indolizidine α,β-unsaturated *N*-acyliminium ion precursor with propargyltrimethylsilane gave an allenyl adduct which could be cyclized with formic acid to a novel bridged tricyclic ketone. Such bridged tricyclic heterocyclic systems would be expected to be very useful scaffolds for the future preparation of libraries of novel compounds for new drug discovery programs. Such investigations are now in progress.

EXPERIMENTAL

General methods. Unless stated, $CDCl_3$ was used as a solvent for all ^1H NMR (δ_H, 500 MHz) and ^{13}C NMR (δ_C, 125 MHz) measurements. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, and br= broard. All coupling constants (*J*) are measured in hertz (Hz). Chemical shifts are reported in parts per million (ppm) from tetramethylsilane and are corrected to 0.00 (TMS) ppm for ^1H NMR and 77.00 ($CDCl_3$ center line) for ^{13}C NMR. ^1H and ^{13}C NMR assignments for all compounds are given in the Supporting Information and are based on COSY, HSQC and HMBC experiments and in some cases NOESY/ROESY experiments. Optical Rotations were

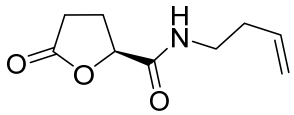
measured at 25 °C in chloroform (λ = 589 nm). Infrared spectra were obtained on neat samples and major bands are reported in wavenumbers (cm^{-1}). High resolution mass spectra (HRMS) were obtained using a Q-TOF mass spectrometer.

All reactions using air/moisture sensitive reagents were performed in an oven dried apparatus, under an atmosphere of dry nitrogen. Anhydrous THF was obtained by distillation from sodium/benzophenone. Anhydrous CH_2Cl_2 and toluene were obtained as commercial samples or from an anhydrous solvent dispenser. Column chromatography was performed using silica gel (35-70 μm) and the solvents specified. Petrol refers to the hydrocarbon fraction of bp 40-60 °C.

Synthesis of *N*-acyliminium ion precursors 3a-f.

Compounds **3a**, **10a** and **10d** were prepared as described previously.[5]

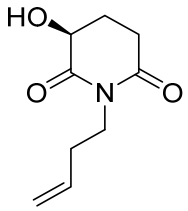
(S)-N-(But-3-en-1-yl)-5-oxotetrahydrofuran-2-carboxamide



To a solution of (*S*)-oxotetrahydrofuran-2-carbonyl chloride[27] (0.950 g, 6.41 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (0.972 g, 9.61 mmol) and 4-butenylamine[5] (0.455 g, 6.41 mmol) at 0 °C. The resulting mixture was stirred at rt for 16 h then it was quenched with water (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3x20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (2:1, EtOAc/petrol) of the crude product afforded the title compound (0.740 g, 63%) as a yellow oil. $[\alpha]_D^{25}$ - 16.8 (*c* 0.8 $CHCl_3$). ν_{max}/cm^{-1} 3012, 1684, 1399, 1375, 1101, 1126, 919. δ_H 6.54 (1H, br. s, N*H*), 5.79-5.71 (1H, m), 5.10 (1H, d, *J* = 17.5 Hz), 5.09 (1H, d, *J* = 10.0 Hz), 4.85 (1H, t, *J* = 7.0 Hz), 3.38 (2H, q, *J* = 6.5 Hz,), 2.66-2.59 (1H, m), 2.57-2.54 (2H, m), 2.39-2.33 (1H, m), 2.31-2.27 (2H, m). δ_C

175.7, 169.1, 134.6, 117.3, 77.3, 38.0, 33.4, 27.3, 25.7. HRMS (ESI) *m/z* calcd for $C_9H_{14}NO_3$ $[M + H]^+$ 184.0974, found 184.0977.

(S)-1-(But-3-en-1-yl)-3-hydroxypiperidine-2,5-dione



(*S*)-*N*-(But-3-en-1-yl)-5-oxotetrahydrofuran-2-carboxamide (0.500 g, 2.73 mmol) was dissolved in THF (20 mL) and the solution was cooled to -78 ^oC. *t*-BuOK (0.153 g, 1.36 mmol) was then added portionwise at this temperature and the resulting suspension was warm to -58 ^oC over 1 h. Water (15 mL) was added and the aqueous layer was extracted with Et_2O (2x20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (1:1, EtOAc/petrol) yielded the desired product (0.334 g, 67%) as a colorless oil. $[\alpha]_D^{25}$ - 22.3 (*c* 0.2 $CHCl_3$). ν_{max}/cm^{-1} 3446, 1683, 1397, 1345, 1172, 1123, 915. δ_H 5.77-5.69 (1H, m), 5.03-5.00 (2H, m), 4.21 (1H, dd, *J* = 5.5, 12.5 Hz), 3.92-3.82 (2H, m), 3.71 (1H, s, OH), 2.90-2.85 (1H, m), 2.67-2.59 (1H, m), 2.33-2.29 (3H, m), 1.93-1.84 (1H, m). δ_C 175.1, 171.1, 134.5, 117.1, 68.2, 39.2, 32.1, 30.7, 25.2. HRMS (ESI) *m/z* calcd for $C_9H_{14}NO_3$ $[M + H]^+$ 184.0974, found 184.0973.

*(S)-3-(Benzyloxy)-1-(but-3-en-1-yl)piperidine-2,6-dione (**9c**).* To a solution of (*S*)-1-(but-3-en-1-yl)-3-hydroxypiperidine-2,5-dione (0.300 g, 1.63 mmol) and BnBr (0.560 g, 3.27 mmol) in Et_2O (30 mL) was added Ag_2O (0.755 g, 3.27 mmol) at rt. The resulting suspension was stirred in the dark at rt for 16 h then filtered through a pad of Celite® using Et_2O as eluent. The residue was concentrated *in vacuo* and purified by column chromatography (1:5, EtOAc/petrol) to give the title compound (0.391 g, 88%) as a colorless oil. $[\alpha]_D^{25}$ - 46.1 (*c* 0.5

$CHCl_3$). ν_{max}/cm^{-1} 1697, 1437, 1353, 1110, 912, 758, 676. δ_H 7.35-7.29 (5H, m), 5.77-5.71 (1H, m), 5.02 (1H, d, *J* = 17.5 Hz), 4.99 (1H, d, *J* = 10.5 Hz), 4.86 (1H, d, *J* = 12.0 Hz), 4.66 (1H, d, *J* = 12.0 Hz), 4.03 (1H, t, *J* = 6.0 Hz), 3.82 (2H, t, *J* = 7.0 Hz), 2.91-2.85 (1H, m), 2.58-2.52 (1H, m), 2.30-2.26 (2H, m), 2.05-2.02 (2H, m) δ_C 171.4, 171.2, 137.1, 134.7, 128.3, 127.8, 127.7, 116.7, 73.6, 72.2, 38.6, 32.6, 28.9, 23.9. HRMS (ESI) *m/z* calcd for $C_{16}H_{20}NO_3$ $[M + H]^+$ 274.1436, found 274.1433.

(4S,5S)-1-(But-3-en-1-yl)-4,5-dihydroxy-5-vinylpyrrolidin-2-one ***(10b).*** To a solution of (*S*)-1-(but-3-en-1-yl)-2,5-dioxopyrrolidin-3-yl acetate[5] (1.200 g, 4.39 mmol) in THF (40 mL) at 0 ^oC was added vinylmagnesium bromide (1.0 M in THF, 13.18 mmol) dropwise. The resulting mixture was stirred at that temperature for a further 2 h before it was quenched with NH_4Cl (saturated aqueous solution). The aqueous layer was extracted with Et_2O (2x20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in *vacuo*. The crude product was purified by column chromatography (1:1.5 EtOAc/petrol) yielding the title compound (0.536 g, 62%) as a colorless oil and as a mixture of diastereomers (23:77). A small amount of each isomer could be obtained in pure form by further separation by column chromatography. Major isomer: $[\alpha]_D^{25}$ + 27.9 (*c* 1.3 $CHCl_3$). ν_{max}/cm^{-1} 3364, 1689, 1395, 1343, 987, 927, 735, 696. δ_H 6.15 (1H, dd, *J* = 10.5, 17.0 Hz), 5.80-5.74 (1H, m), 5.78 (1H, d, *J* = 17.0 Hz), 5.58 (1H, d, *J* = 10.5 Hz), 5.15-5.05 (2H, m), 4.60 (1H, t, *J* = 5.0 Hz), 3.47 (1H, quintet, *J* = 6.5 Hz), 3.04 (1H, quintet, *J* = 6.5 Hz), 2.90 (1H, s, OH), 2.76 (1H, dd, *J* = 6.5, 17.0 Hz), 2.40 (1H, dd, *J* = 5.0, 17.0 Hz), 2.35-2.30 (2H, m); δ_C 172.8, 134.2, 136.1, 117.3, 117.0, 92.5, 70.4, 38.4, 36.0, 31.3. HRMS (ESI) *m/z* calcd for $C_{10}H_{16}NO_3$ $[M + H]^+$ 198.1173, found 198.1176. Minor isomer: $[\alpha]_D^{25}$ + 32.8 (*c* 0.6 $CHCl_3$). ν_{max}/cm^{-1} 3324, 1669, 1399, 1091, 986, 921, 730, 691. δ_H 5.78-5.72 (2H, m), 5.51 (1H, d, *J* = 17.0 Hz), 5.36 (1H, d, *J* = 11.5 Hz), 5.04 (1H, d, *J* = 17.0 Hz), 4.99 (1H, d, *J* = 10.0 Hz), 4.58 (1H, m), 3.78 (1H, s, OH), 3.40 (1H, quintet, *J* = 7.0 Hz), 3.01 (1H, quintet, *J* = 7.0 Hz,), 2.55 (1H, dd, *J* = 7.0,

17.5 Hz), 2.47 (1H, dd, *J* = 3.5, 17.5 Hz), 2.37-2.33 (2H, m); δ_C 171.6, 136.4, 135.6, 118.3, 116.2, 90.3, 73.7, 39.1, 35.7, 33.4.

(5S,6S)-5-(Benzyloxy)-1-(but-3-en-1-yl)-6-hydroxy-6-vinylpiperidin-2-one ***(10c).*** The title compound was prepared in an analogous fashion to **10b** described above, from **9c** (0.350 g, 1.28 mmol), THF (15 mL) and vinylmagnesium bromide (1.0 M in THF, 1.92 mmol). The crude product was purified by column chromatography (1:1, EtOAc/petrol) yielding the title compound (0.215 g, 56%) as a colorless oil. $[\alpha]_D^{25}$ + 48.9 (*c* 4.1 $CHCl_3$). ν_{max}/cm^{-1} 3293, 1634, 1452, 1398, 1080, 989, 759, 721. δ_H 7.37-7.32 (5H, m), 5.79-5.72 (2H, m), 5.38 (1H, d, *J* = 17.5 Hz), 5.36 (1H, d, *J* = 10.5 Hz), 4.99 (1H, d, *J* = 17.0 Hz), 4.93 (1H, d, *J* = 10.0 Hz), 4.67 (1H, d, *J* = 12.0 Hz), 4.51 (1H, d, *J* = 12.0 Hz), 4.01 (1H, s, OH), 3.62-3.56 (2H, m), 3.07-3.01 (1H, m), 2.60-2.54 (1H, m), 2.41-2.37 (1H, m), 2.31-2.28 (2H, m), 2.02-1.96 (1H, m), 1.91-1.86 (1H, m). δ_C 169.5, 137.8, 136.8, 136.0, 128.4, 128.0, 127.5, 118.7, 115.7, 87.4, 76.3, 71.3, 41.9, 33.4, 26.6 19.0. HRMS (ESI) *m/z* calcd for $C_{18}H_{24}NO_3$ $[M + H]^+$ 302.1730, found 302.1735.

(1S,8aS)-1,8a-Dihydroxy-1,5,6,8a-tetrahydroindolizin-3(2H)-one ***(3b).*** To a solution of the diene **10b** (0.100 g, 0.50 mmol) in CH_2Cl_2 (10 mL) under an atmosphere of nitrogen was added Grubbs' 2nd generation catalyst (0.008 g, 0.01 mmol). The reaction mixture was stirred at rt for 2 h and then concentrated in *vacuo*. Column chromatography (1:49 MeOH/EtOAc) of the crude product mixture afforded the title compound (0.059 g, 70%) as a yellow oil. $[\alpha]_D^{25}$ + 46.5 (*c* 0.8 $CHCl_3$). ν_{max}/cm^{-1} 3356, 1669, 1362, 1023, 1072, 700. δ_H (300 MHz) 6.07-5.95 (1H, m), 5.84 (1H, d, *J* = 10.2 Hz), 4.13 (2H, m), 3.15 (1H, dd, *J* = 4.5, 16.0 Hz), 2.65 (1H, dd, *J* = 16.0, 7.5 Hz), 2.44 (1H, dd, *J* = 16.0, 7.5 Hz), 2.17-2.05 (2H, m). δ_C (75 MHz) 171.1, 128.7, 126.9, 83.7, 70.8, 38.5, 33.2, 24.1. HRMS (ESI) *m/z* calcd for $C_8H_{12}NO_3$ $[M + H]^+$ 170.0721, found 170.0723.

(1S,9aS)-1-(Benzyloxy)-9a-hydroxy-1,2,3,6,7,9a-hexahydro-4H-quinolizin-4-one ***(3c).*** The title compound was prepared in an analogous fashion to **3b** described above, from the diene **10c** (0.150 g, 0.49 mmol), CH_2Cl_2 (10 mL) and Grubbs' 2nd generation catalyst (0.012 g, 0.01 mmol). The reaction mixture was stirred at rt for 1 h and then concentrated in *vacuo*. The crude product was purified by column chromatography (2:1 EtOAc/petrol) yielding the title compound (0.092 g, 68%) as a pale yellow oil. $[\alpha]_D^{25}$ + 48.9 (*c* 4.1 $CHCl_3$). ν_{max}/cm^{-1} 3357, 1662, 1371, 1080, 1024, 989, 759, 702. δ_H 7.31-7.25 (5H, m), 5.94-5.91 (1H, m),5.85 (1H, d, *J* = 10.0 Hz), 4.65 (1H, d, *J* = 12.0 Hz), 4.53 (1H, dd, *J* = 6.0, 13.0 Hz), 4.49 (1H, d, *J* = 12.0 Hz), 3.45 (1H, dd, *J* = 3.5, 10.0 Hz), 3.33 (1H, s, OH), 3.00 (1H, ddd, *J* = 6.0, 13.0 Hz), 2.56 (1H, dt, *J* = 5.5, 17.5 Hz), 2.28-2.21 (1H, m), 2.16-2.08 (1H, m), 2.07-2.00 (1H, m), 1.96-1.91 (1H, m), 1.88-1.83 (1H, m). δ_C 169.7, 137.1, 129.6, 128.5, 128.2, 128.1, 127.9, 80.9, 77.5, 71.7, 34.6, 29.2, 24.6, 20.3. HRMS (ESI) *m/z* calcd for $C_{16}H_{20}NO_3$ $[M + H]^+$ 274.1482, found 274.1487.

(1S,9aS)-1-(Benzyloxy)-9a-hydroxy-1,2,5,6,7,9a-hexahydro-3H-pyrrolo[1,2-a]azepin-3-one ***(3d).*** The title compound was prepared in an analogous fashion to **3b** described above, from the diene **10d**[5] (0.340 g, 1.12 mmol), CH_2Cl_2 (20 mL) and Grubbs' 2nd generation catalyst (0.028 g, 0.03 mmol). The reaction mixture was stirred at rt for 2 h and then concentrated in *vacuo*. Column chromatography (2:1 EtOAc/petrol to EtOAc, silica gel was neutralized first with ammonia) of the crude reaction mixture afforded the title compound (0.273 g, 89%) as a brown oil. This compound was prone to dehydration to give diene **11** upon storage. $[\alpha]_D^{25}$ + 33.8 (*c* 0.7 $CHCl_3$). ν_{max}/cm^{-1} 3356, 1669, 1363, 1073, 1023, 699. δ_H 7.37 – 7.28 (5H, m), 5.99 – 5.94 (1H, m), 5.91 (1H, d, *J* = 11.9 Hz), 4.68 (1H, d, *J* = 12.0 Hz), 4.62 – 4.57 (2H, m), 3.99 (1H, t, *J* = 5.5 Hz), 3.94 (1H, dd, *J* = 13.0, 6.5 Hz), 3.17 – 3.09 (1H, m), 2.67 (1H, dd, *J* = 16.5, 7.0 Hz), 2.30 (1H, dd, *J* = 16.5, 5.5 Hz), 2.18 (1H, m), 1.83 (2H, m); δ_C 171.3,

137.5, 133.8, 128.4, 128.3, 127.8, 127.5, 93.1, 81.4, 72.3, 37.4, 36.2, 26.0, 25.5. HRMS (ESI) *m/z* calcd for $C_{16}H_{20}NO_3$ $[M + H]^+$ 274.1456, found 274.1458.

(1S,8aS)-8a-Hydroxy-1-((triisopropylsilyl)oxy)-1,5,6,8a-tetrahydroindolizin-3(2H)-one ***(3e).*** Compound **3b** (0.132 g, 0.78 mmol) was dissolved in CH_2Cl_2 (10 mL) and was treated with TIPSOTf (0.361 g, 1.18 mmol) and 2,6-lutidine (0.200 g, 1.18 mmol) at 0 ^oC. The ice bath was then removed and the reaction mixture was stirred at rt for 30 min. A saturated aqueous solution of $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in *vacuo*. The crude product was purified by column chromatography (1:5 EtOAc/petrol) yielding the title compound (0.306 g, 80%) as a colorless oil. $[\alpha]_D^{25}$ + 14.2 (*c* 0.2 $CHCl_3$). ν_{max}/cm^{-1} 3296, 1702, 1357, 1023, 1014, 692. δ_H 5.96 (1H, m), 5.84 (1H, d, *J* = 10.0 Hz), 4.27 (1H, t, *J* = 7.5 Hz), 4.15 (2H, m), 3.10 (1H, td, *J* = 12.0, 5.0 Hz), 2.67 (1H, dd, *J* = 16.0, 7.5 Hz), 2.54 (1H, dd, *J* = 16.0, 7.5 Hz), 2.22 – 2.13 (1H, m), 2.10 – 2.05 (1H, m), 1.07 (21H, s). δ_C 169.9, 128.1, 127.9, 83.6, 71.5, 39.4, 33.5, 23.9, 17.7, 11.6. HRMS (ESI) *m/z* calcd for $C_{17}H_{32}NO_3Si$ $[M + H]^+$ 326.2136, found 326.2139.

(1S,8aS)-8a-Hydroxy-3-oxo-1,2,3,5,6,8a-hexahydroindolizin-1-yl acetate ***(3f).*** To a solution of diol **3b** (0.104 g, 0.60 mmol) in pyridine (10 mL) was added Ac_2O (0.080 g, 0.80 mmol) at rt and the resulting solution was stirred at rt for 16 h. CH_2Cl_2 (10 mL) and $CuSO_4$ (10 mL, saturated aqueous solution) were added and the organic layer washed with $CuSO_4$ (3x10 mL) and then with brine (2x10 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc) of the crude product gave the title compound (0.106 g, 84%) as a colorless oil. $[\alpha]_D^{25}$ + 32.4 (*c* 0.2 $CHCl_3$). ν_{max}/cm^{-1} 3365, 2980, 1745, 1653, 1350, 1021, 697. δ_H 5.99 (2H, broad s), 5.11 (1H, t, *J* = 8.0 Hz), 4.16 (1H, dd, *J* = 13.0, 6.5 Hz), 3.14 – 3.07 (1H, m), 2.80 (1H, dd, *J* = 16.8, 8.0 Hz), 2.66 (1H, dd, *J* = 16.8, 7.5 Hz),

2.17 (3H, s), 2.15-2.07 (2H, m). δ_C 171.0, 169.7, 129.3, 127.3, 84.1, 71.4, 35.6, 33.2, 23.95, 21.0. LRMS (ESI) *m/z* 212 $[M + H]^+$

Synthesis of *N*-acyliminium ion precursors 13-15.

*(S)-1-(Benzyloxy)-1,2,5,6-tetrahydro-3H-pyrrolo[1,2-a]azepin-3-one (**11**).* To a solution of the diene **10b**[5] (0.500 g, 1.66 mmol) in CH_2Cl_2 (30 mL) under an atmosphere of nitrogen was added Grubbs' 1st generation catalyst (0.040 g, 0.04 mmol). The resulting mixture was stirred at rt for 2 h and then treated with *p*-toluenesulfonic acid monohydrate (0.030 g, 0.16 mmol) for 30 min at rt. The reaction mixture was concentrated in *vacuo* and subjected to column chromatography (1:2 EtOAc/petrol) to afford the title compound (0.343 g, 81%) as a light brown oil. $[\alpha]_D^{25}$ + 22.9 (*c* 0.5 $CHCl_3$). ν_{max}/cm^{-1} 1695, 1407, 1338, 1108, 919, 740, 692. δ_H δ 7.37 – 7.28 (5H, m), 5.92 – 5.81 (2H, m), 5.33 (1H, d, *J* = 7.0 Hz), 4.60 (2H, app. q, *J* = 12.0 Hz), 4.50 (1H, d, *J* = 5.0 Hz), 3.86 (1H, dd, *J* = 12.0, 6.5 Hz), 3.56 (1H, dd, *J* = 12.0, 8.0 Hz), 2.72 (1H, dd, *J* = 17.5, 5.0 Hz), 2.57 (1H, dd, *J* = 17.5, 2.0 Hz), 2.50 (1H, t, *J* = 6.5 Hz), 2.44 – 2.38 (1H, m). δ_C 172.6, 142.8, 137.5, 130.6, 128.6, 127.9, 127.8, 124.1, 102.8, 73.2, 70.6 , 41.0, 37.5, 30.4. HRMS (ESI) *m/z* calcd for $C_{16}H_{18}NO_2$ $[M + H]^+$ 256.1387, found 256.1388.

Synthesis of 13 and 14 via the endoperoxide 12 (Scheme 4). A two-necked round bottom flask equipped with a condenser was charged with diene **11** (0.300 g, 1.15 mmol), *meso*-tetraphenylporphyrin (0.021 g, 0.03 mmol) and CH_2Cl_2 (30 mL). The mixture was radiated with a 500 W flood light while bubbling O_2 gas through the reaction solution. After 2 h TLC analysis indicated the total consumption of the diene to the endoperoxide. At this stage a small amount of the reaction mixture was taken then concentrated and subjected to column chromatography (1:1 EtOAc/petrol) to obtain a pure sample of the endoperoxide **12**. Thiourea (0.087 g, 1.15 mmol) was added to the remaining solution and the mixture was stirred at rt for 18 h. The reaction mixture was concentrated in *vacuo* and subjected to column

chromatography (1:49 MeOH/EtOAc) to afford the diol **14** (0.114 g, 41%) and ketone **13** (0.093 g, 28%) both as a colorless oils. **Endoperoxide (12):** $[\alpha]_D^{25}$ + 32.8 (*c* 0.4 $CHCl_3$). ν_{max}/cm^{-1} 1717, 1669, 1370, 1091, 1073, 735, 697. δ_H 7.47 – 7.26 (5H, m), 6.72 – 6.67 (1H, m), 6.64 (1H, d, *J* = 9.4 Hz), 4.87 (1H, t, *J* = 6.0 Hz), 4.62 (1H, d, *J* = 11.6 Hz), 4.55 (1H, d, *J* = 11.6 Hz), 4.05 (1H, dd, *J* = 12.4, 6.0 Hz), 2.82 (1H, dd, *J* = 17.5, 6.4 Hz), 2.70 (1H, td, *J* = 13.2, 4.7 Hz), 2.47 (1H, d, *J* = 17.5 Hz), 2.38 – 2.31 (1H, m), 2.09 (1H, dt, *J* = 15.1, 5.2 Hz). δ_C 171.9, 136.7, 130.3, 128.7, 128.3, 127.9, 123.3, 96.6, 76.5, 75.0, 72.3, 36.6, 34.1, 34.1. HRMS (ESI) *m/z* calcd for $C_{16}H_{17}NO_4Na$ $[M + Na]^+$ 310.2147, found 310.2148. **Ketone (13):** $[\alpha]_D^{25}$ + 17.3 (*c* 0.4 $CHCl_3$). ν_{max}/cm^{-1} 3446, 1688, 1398, 1345, 1187, 1115, 907. δ_H 7.40-7.26 (5H, m), 6.43 (1H, d, *J* = 13.0 Hz), 6.07 (1H, d, *J* = 13.0 Hz), 4.61 (1H, d, *J* = 12.0 Hz), 4.51 (1H, d, *J* = 12.0 Hz), 4.09 – 4.07 (1H, m), 3.98 – 3.92 (1H, m), 3.48 – 3.35 (1H, m), 2.89 – 2.71 (3H, m), 2.44 (1H, d, *J* = 17.0 Hz). δ_C 200.6, 172.6, 139.6, 137.0, 131.3, 128.7, 128.2, 127.8, 93.2, 80.0, 71.9, 43.4, 35.6, 33.2. LRMS (ESI) *m/z* 288 $[M + H]^+$. **Diol (14):** $[\alpha]_D^{25}$ + 52.6 (*c* 0.9 $CHCl_3$). ν_{max}/cm^{-1} 3446, 1689, 1403, 1347, 1191, 1117, 911. δ_H 7.41 – 7.27 (5H, m), 6.24 (1H, d, *J* = 12.0 Hz), 6.08 (1H, dd, *J* = 12.0, 5.5 Hz), 4.70 (1H, d, *J* = 12.0 Hz), 4.61 (1H, d, *J* = 12.0 Hz), 4.48 (1H, d, *J* = 12.0, 5.5 Hz), 4.06 – 3.98 (2H, m), 3.43 – 3.37 (1H, m), 2.67 (1H, dd, *J* = 16.5, 7.5 Hz), 2.33 (1H, dd, *J* = 16.5, 7.5 Hz), 1.96 (2H, d, *J* = 5.0 Hz). δ_C 170.3, 137.5, 136.6, 130.6, 128.6, 128.0, 127.8, 91.5, 80.5, 72.5, 66.8, 36.2, 33.6, 33.0. HRMS (ESI) *m/z* calcd for $C_{16}H_{20}NO_4$ $[M + H]^+$ 290.1362, found 290.1367. Key NOESY correlation for **14**: H9 (6.24 ppm) to CH_2Ph (4.70 ppm).

(1S,7S,9aS)-1-(Benzyloxy)-7,9a-dihydroxy-1,2,5,6,7,9a-hexahydro-3H-pyrrolo[1,2-a]azepin-3-one ***(15).*** The enone **13** (0.050 g, 0.17 mmol) was dissolved in MeOH (2 mL) and treated with $NaBH_4$ (0.032 g, 0.87 mmol) at 0 ^oC for 3 h. A saturated aqueous solution of $NaHCO_3$ (2 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2x3 mL). The combined

organic layers were dried ($MgSO_4$) and concentrated in *vacuo*. The crude product was purified by column chromatography (1:49 MeOH/EtOAc) yielding the title compound (0.034 g, 70%) as a colorless oil. $[\alpha]_D^{25}$ + 10.8 (*c* 0.2 $CHCl_3$). ν_{max}/cm^{-1} 3460, 1675, 1387, 1345, 1201, 1190, 912. δ_H 7.36 – 7.25 (5H, m), 6.02 – 5.97 (2H, m), 4.62 – 4.59 (2H, m), 4.57 (1H, d, *J* = 12.0 Hz), 4.48 – 4.41 (1H, m), 3.94 (1H, m), 3.19 – 3.11 (1H, m), 2.65 (1H, dd, *J* = 17.0, 9.0 Hz), 2.29 (1H, dd, *J* = 17.0, 5.0 Hz), 1.94 – 1.88 (2H, m). δ_C 171.3, 136.7, 135.8, 130.3, 128.8, 128.1, 127.5, 90.4, 78.9, 71.6, 66.4, 36.6, 33.7, 33.1. HRMS (ESI) *m/z* calcd for $C_{16}H_{20}NO_4$ $[M + H]^+$ 290.1362, found 290.1366.

Synthesis of bridged tricyclics 5a-c−8a-c and 17a-c and 18a-c.

*(1S,7R,10aS)-1-(Benzyloxy)-7,8,9,10-tetrahydro-1H-7,10a-methanopyrrolo[1,2-a]azocin-3(2H)-one (**5a**) and (1S,7S,10aR)-1-(benzyloxy)-7,8,9,10-tetrahydro-1H-7,10a-methanopyrrolo[1,2-a]azocin-3(2H)-one (**6a**).* To a solution of **3a** (0.150 g, 0.578 mmol) and allyltrimethylsilane (0.079 g, 0.694 mmol) in CH_2Cl_2 (6 mL) was added BF_3•Et_2O (0.164 g, 1.156 mmol) dropwise at 0 °C. The reaction mixture was stirred at rt for 18 h and quenched with saturated $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3x5 mL) and the combined organic layers was dried ($MgSO_4$) and then concentrated *in vacuo*. Column chromatography (1:1 EtOAc/petrol) of the crude reaction mixture gave a 1:1 mixture of the title compounds (0.111 g, 68%) as a colorless oil A small amount of each isomer could be obtained in pure form by further separation by column chromatography. **5a**: $[\alpha]_D^{25}$ - 9.3 (*c* 6.3 $CHCl_3$). ν_{max}/cm^{-1} 2930, 1684, 1638, 1405, 1369, 1070, 738, 697. δ_H 7.35-7.28 (5H, m), 7.04 (1H, d, *J* = 8.0 Hz), 5.06 (1H, t, *J* = 8.0 Hz), 4.58 (1H, d, *J* = 12.0 Hz), 4.43 (1H, d, *J* = 12.0 Hz), 3.71 (1H, d, *J* = 5.0 Hz), 2.73 (1H, dd, *J* = 5.0, 17.5 Hz), 2.63-2.62 (1H, m), 2.46 (1H, d, *J* = 17.5 Hz), 2.10 (1H, d, *J* = 12 Hz), 1.66-1.63 (1H, m), 1.61-1.52 (5H, m), 1.44 (1H, d, *J* = 12.0 Hz). δ_C 169.4, 137.8, 128.4, 127.7, 127.3, 123.4, 110.9, 79.2, 71.1, 63.9,

37.5, 36.3, 30.1, 29.7, 29.4, 18.2. LRMS (ESI) *m/z* $[M + H]^+$ 284. **6a:** $[\alpha]_D^{25}$ + 91.1 (*c* 4.2 $CHCl_3$). ν_{max}/cm^{-1} 2926, 1696, 1636, 1401, 1331, 1097, 734, 697. δ_H (300 MHz) 7.39-7.30 (5H, m), 7.03 (1H, d, *J* = 7.0 Hz), 5.06 (1H, t, *J* = 7.0 Hz), 4.58 (2H, s), 3.81 (1H, t, *J* = 9.0 Hz), 2.57 (1H, s), 2.55 (2H, m), 2.04 (1H, d, *J* = 12.0 Hz), 1.77-1.72 (2H, m), 1.64-1.56 (4H, m), 1.43 (1H, d, *J* = 12.0 Hz). δ_C 166.6, 138.3, 128.0, 127.9, 127.7, 123.3, 109.5, 80.9, 71.8, 60.9, 35.4, 35.2, 31.6, 30.2, 29.9, 18.3. HRMS (ESI) *m/z* calcd for $C_{18}H_{22}NO_2$ $[M + H]^+$ 284.1647, found 284.1639. Key NOESY correlation for **6a**: H1 (3.81 ppm) to H11 (1.43 ppm). Compounds **5a** and **6a** had spectroscopic data identical to those reported earlier.[5]

*(1S,7R,10aS)-1-((Triisopropylsilyl)oxy)-1,2,7,8,910-hexahydro-3H-7,10a-methanopyrrolo[1,2-a]azocin-3-one (**5b**) and (1S,7S,10aR)-1-((triisopropylsilyl)oxy)-1,2,7,8,910-hexahydro-3H-7,10a-methanopyrrolo[1,2-a]azocin-3-one (**6b**).* Prepared in a similar fashion to **5a**/**6a** above, from **3e** (0.100 g, 0.30 mmol), allyltrimethylsilane (0.042 g, 0.36 mmol), CH_2Cl_2 (4 mL) and BF_3•Et_2O (0.086 g, 0.61 mmol). Column chromatography (1:3 EtOAc/petrol) of the crude product gave a 1:1 mixture of the title compound (0.081 g, 78%) as a colorless oil. A small amount of each isomer could be obtained in pure form by further separation by column chromatography. **5b**: $[\alpha]_D^{25}$ - 13.6 (*c* 0.6 $CHCl_3$). ν_{max}/cm^{-1} 2980, 1653, 1350, 1021, 697. δ_H 7.05 (1H, d, *J* = 7.0 Hz), 5.06 (1H, t, *J* = 7.0 Hz), 4.14 (1H, d, *J* = 9.0 Hz), 2.55 (1H, s), 2.54 (2H, d, *J* = 9.0 Hz), 2.01 (1H, d, *J* = 12.0 Hz), 1.71 (1H, s), 1.55 (5H, s), 1.73 (21H, s). δ_C 168.2, 123.0, 111.5, 75.6, 62.7, 39.0, 35.4, 31.1, 30.3, 29.8, 18.3, 18.1, 12.3. LRMS (ESI) *m/z* 350 $[M + H]^+$. **6b**: $[\alpha]_D^{25}$ + 83.4 (*c* 0.7 $CHCl_3$). ν_{max}/cm^{-1} 2917, 1645, 1357, 1071, 692. δ_H 7.06 (1H, d, *J* = 7.0 Hz), 5.06 (1H, t, *J* = 7.0 Hz), 4.12 (1H, t, *J* = 4.5 Hz), 2.84 (1H, dd, *J* = 17.0, 4.5 Hz), 2.63 (1H, s), 2.27 (1H, d, *J* = 17.0 Hz), 2.00 (1H, d, *J* = 12.0 Hz), 1.65 (1H, d, *J* = 12.0 Hz), 1.57 (5H, m), 1.42 (1H, d, *J* = 12.0 Hz), 1.07 (21H,

s); δ_C 169.7, 123.7, 110.9, 73.9, 64.8, 40.8, 37.4, 30.4, 30.2, 29.8, 18.5, 18.2, 12.5. LRMS (ESI) *m/z* 350 $[M + H]^+$.

*(1S,7R,10aS)-3-Oxo-2,3,7,8,9,10-hexahydro-1H-7,10a-methanopyrrolo[1,2-a]azocin-1-yl acetate (**5c**) and (1S,7S,10aR)-3-oxo-2,3,7,8,9,10-hexahydro-1H-7,10a-methanopyrrolo[1,2-a]azocin-1-yl acetate (**6c**).* Prepared in a similar fashion to **5a**/**6a** above, from **3f** (0.100 g, 0.30 mmol), allyltrimethylsilane (0.042 g, 0.36 mmol), CH_2Cl_2 (4 mL) and BF_3•Et_2O (0.086 g, 0.61 mmol). Column chromatography (1:3 EtOAc/petrol) of the crude product gave a 1:1 mixture of the title compounds (0.081 g, 78%) as a colorless oil. A small amount of each isomer could be obtained in pure form by further separation by column chromatography. **5c:** $[\alpha]_D^{25}$ -17.4 (*c* 0.6 $CHCl_3$). ν_{max}/cm^{-1} 2922, 1706, 1692, 1352, 1028, 1004, 642. δ_H 6.99 (1H, d, *J* = 7.5 Hz), 5.02 (1H, t, *J* = 7.5 Hz), 4.93 (1H, d, *J* = 8.0 Hz), 2.69 (1H, dd, *J* = 16.5, 8.0 Hz), 2.54-2.50 (2H, m), 2.05 (3H, s), 1.91 (1H, d, *J* = 12.0 Hz), 1.70 (1H, d, *J* = 12.0 Hz), 1.58 – 1.43 (6H, m). δ_C 170.4, 167.1, 122.9, 111.5, 74.9, 61.3, 35.3, 35.2, 32.1, 29.8, 29.7, 21.0, 18.2. HRMS (ESI) *m/z* calcd for $C_{13}H_{17}NO_3Na$ $[M + Na]^+$ 258.1106, found 258.1119. **6c**: $[\alpha]_D^{25}$ +72.8 (*c* 0.2 $CHCl_3$). δ_H 7.07 (1H, d, *J* = 8.0 Hz), 5.14-5.10 (2H, m,), 2.94 (1H, dd, *J* = 18.0, 5.5 Hz), 2.64 (1H, s), 2.34 (1H, d, *J* = 18.0 Hz), 2.08 (3H, s), 1.73 (1H, d, *J* = 11.5 Hz), 1.66 – 1.57 (7H, m). δ_C 170.5, 168.2, 123.5, 111.2, 74.0, 63.1, 37.0, 36.9, 30.0, 29.6, 29.4, 20.9, 18.2. HRMS (ESI) *m/z* calcd for $C_{13}H_{17}NO_3Na$ $[M + Na]^+$ 258.1106, found 258.1118.

*(1S,7R)- and (1S,7S)-7-Allyl-1-(benzyloxy)-1,5,6,7-tetrahydroindolizin-3(2H)-one (**16**).* To a solution of **3a** (0.050 g, 0.19 mmol) and allyltributyltin (0.075 g, 0.23 mmol) in CH_2Cl_2 (2 mL) was added BF_3•Et_2O (0.053 g, 0.38 mmol) dropwise at 0 °C. The reaction mixture was stirred at rt for 18 h and quenched with saturated $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3x5 mL) and the combined organic layers were dried ($MgSO_4$) and then concentrated *in vacuo*. Column chromatography (1:2 EtOAc/petrol) of the

crude product gave a 1:1 mixture of the title compounds (0.039 g, 72%) as a colorless oil. A small amount of each isomer could be obtained in pure form by further separation by column chromatography. (1*S,7R*)-**16** could be converted to **5a** and (1*S,7S*)-**16** to **6a** upon treatment with BF_3•Et_2O. (1*S,7R*)-**16**: $[\alpha]_D^{25}$ + 31.5 (*c* 0.2 $CHCl_3$). ν_{max}/cm^{-1} 2928, 1717, 1669, 1370, 1091, 1070, 735, 697. δ_H 7.37-7.25 (5H, m), 5.83-5.78 (1H, m), 5.10-5.007 (3H, m), 4.59 (2H, app. q, *J* = 11.5 Hz), 4.52 (1H, d, *J* = 6.5 Hz), 3.72-3.67 (1H, m), 3.40-3.35 (1H, m), 2.68 (1H, dd, *J* = 6.5, 17.0 Hz), 2.51 (1H, d, *J* = 17.0 Hz), 2.36 (1H, br. s), 2.19-2.11 (2H, m), 1.87-1.83 (1H, m), 1.58-1.52 (1H, m). δ_C 171.5, 138.7, 137.5, 136.0, 128.5, 127.8, 127.7, 116.7 , 105.9, 71.6, 70.4, 40.1, 37.5, 37.1, 32.1, 26.1. HRMS (ESI) *m/z* calcd for $C_{18}H_{22}NO_2$ $[M + H]^+$ 284.1645, found 284.1651. (1*S,7S*)-**16**: $[\alpha]_D^{25}$ - 0.5 (*c* 0.2 $CHCl_3$). ν_{max}/cm^{-1} 2917, 1717, 1671, 1406, 1369, 1088, 1068, 735, 697. δ_H 7.37-7.30 (5H, m), 5.82-5.76 (1H, m,), 5.08-5.00 (3H, m), 4.59 (2H, app. q, *J* = 12.0 Hz), 4.52 (1H, d, *J* = 6.5 Hz), 3.81-3.78 (1H, m), 3.34-3.29 (1H, m), 2.68 (1H, dd, *J* = 6.5, 17.0 Hz), 2.53 (1H, d, *J* = 17.0 Hz), 2.41 (1H, br. s), 2.13 (2H, br. s), 1.93-1.89 (1H, m), 1.43-1.38 (1H, m); δ_C 171.6 , 138.8, 137.5, 135.9 , 128.5, 127.9, 127.8, 116.8 , 106.0, 71.7, 70.6, 39.9, 37.5, 37.4, 32.1, 26.2. HRMS (ESI) *m/z* calcd for $C_{18}H_{21}NO_2Na$ $[M + Na]^+$ 306.1478, found 306.1470.

*(1S,7R,9R,10aS)-1-(Benzyloxy)-9-methyl-7,8,9,10-tetrahydro-1H-7,10a-methanopyrrolo[1,2a]azocin-3(2H)-one (**7a**) and (1S,7S,9S,10aR)-1-(benzyloxy)-9-methyl-7,8,9,10-tetrahydro-1H-7,10a-methanopyrrolo[1,2a]azocin-3(2H)-one (**8a**).* The title compounds were prepared in a similar fashion to **5a**/**6a** above, from **3a** (0.120 g, 0.463 mmol), metallyltrimethylsilane (0.071 g, 0.555 mmol), CH_2Cl_2 (5 mL) and BF_3•Et_2O (0.131 g, 0.926 mmol). Column chromatography (1:1 EtOAc/petrol) of the crude product gave a 1:1 mixture of the title compounds (0.104 g, 76%) as a colorless oil A small amount of each isomer could be obtained in pure form by further separation by column chromatography. **7a**: $[\alpha]_D^{25}$ - 1.6 (*c* 0.3 $CHCl_3$). ν_{max}/cm^{-1} 2922, 1680, 1600, 1435, 1377, 1071, 749, 683.δ_H 7.36-

7.29 (5H, m), 6.99 (1H, d, *J* = 7.5 Hz), 5.11 (1H, t, *J* = 7.5 Hz), 4.60 (1H, d, *J* = 12.0 Hz), 4.44 (1H, d, *J* = 12.0 Hz), 3.73 (1H, d, *J* = 5.0 Hz), 2.75 (1H, dd, *J* = 5.0, 17.5 Hz), 2.61 (1H, br s), 2.48 (1H, d, *J* = 17.5 Hz), 2.10 (1H, d, *J* = 13.0 Hz), 1.82-1.79 (1H, m), 1.67 (2H, br s), 1.60 (1H, d, *J* = 13.0 Hz), 1.26-1.17 (1H, m), 1.10 (1H, t, *J* = 13.0 Hz), 0.86 (3H, d, *J* = 6.5 Hz). δ_C 169.5, 137.9, 128.5, 127.8, 127.5, 123.1, 111.9, 79.2, 71.1, 64.5, 46.2, 39.3, 36.3, 29.7, 29.5, 24.7, 21.5. LRMS (ESI) *m/z* $[M + H]^+$ 298. **8a**: $[\alpha]_D^{25}$ + 67.5 (*c* 0.3 $CHCl_3$). ν_{max}/cm^{-1} 2928, 1677, 1415, 1349, 1079, 768, 698. δ_H 7.38-7.30 (5H, m), 6.97 (1H, d, *J* = 8.0 Hz), 5.09 (1H, t, *J* = 8.0 Hz), 4.61 (1H, d, *J* = 12.0 Hz), 4.57 (1H, d, *J* = 12.0 Hz), 3.83 (1H, t, *J* = 9.0 Hz), 2.56 (2H, d, *J* = 17.0 Hz), 2.53 (1H, br s), 1.95 (1H, d, *J* = 12.0 Hz), 1.81-1.76 (2H, m), 1.63 (1H, d, *J* = 13.0 Hz), 1.42 (1H, d, *J* = 12.0 Hz), 1.38 (1H, t, *J* = 13.0 Hz), 1.89 (1H, dt, *J* = 3.0, 13.0 Hz), 0.92 (3H, d, *J* = 6.0 Hz). δ_C 167.7, 137.6, 128.4, 127.9, 127.5, 122.3, 111.9, 80.6, 72.3, 62.0, 40.0, 39.0, 35.6, 35.2, 29.8, 24.6, 21.7. HRMS (ESI) *m/z* calcd for $C_{19}H_{24}NO_2$ $[M + H]^+$ 298.1776, found 298.1789. Key NOESY correlations for **8a**: H1 (3.81 ppm) to H11 (1.42 ppm) and CH_3 (0.92 ppm) to H11 (1.95 ppm and 1.42 ppm). Compounds **7a** and **8a** had spectroscopic data identical to those reported earlier.[5]

(1S,7R,9R,10aS)-1-(Benzyloxy)-9-phenyl-1,2,7,8,9,10-hexahydro-3H-7,10a-methanopyrrolo[1,2-a]azocin-3-one ***(7b)*** *and (1S,7R,9R,10aS)-1-(benzyloxy)-9-phenyl-1,2,7,8,9,10-hexahydro-3H-7,10a-methanopyrrolo[1,2-a]azocin-3-one* ***(8b)*** *and (1S)-1-(benzyloxy)-9-phenyl-1,2,7,10-tetraahydro-3H-7,10a-methanopyrrolo[1,2-a]azocin-3-one* ***(19).*** The title compounds were prepared in a similar fashion to **5a**/**6a** above, from **3a** (0.050 g, 0.19 mmol), trimethyl(2-phenylallyl)silane[3] (0.044 g, 0.23 mmol), CH_2Cl_2 (2 mL) and BF_3•Et_2O (0.053 g, 0.38 mmol). Column chromatography (1:2 EtOAc/petrol) of the crude product gave a 7:3 mixture of **7b** and **8b**, respectively (0.041 g, 61%) as a colorless oil and compound **19** (0.007 g, 5%, ca 80% pure) as a colorless oil. A small amount of **7b** could be obtained in pure form by further separation by column chromatography. **7b**: $[\alpha]_D^{25}$ + 34.1 (*c*

0.3 $CHCl_3$). ν_{max}/cm^{-1} 2928, 1675, 1415, 1347, 1072, 763, 692. δ_H 7.37-7.54 (10H, m), 7.09 (1H, d, *J* = 8.5 Hz), 4.82 (1H, t, *J* = 8.5 Hz), 4.62 (1H, d, *J* = 12.0 Hz), 4.45 (1H, d, *J* = 12.0 Hz), 3.81 (1H, d, *J* = 5.0 Hz), 2.94 (1H, d, *J* = 12.5 Hz), 2.80 (1H, dd, *J* = 5.0, 17.5 Hz), 2.73 (1H, s), 2.52 (1H, d, *J* = 17.5 Hz), 2.25 (1H, d, *J* = 12.5 Hz), 2.01-1.98 (1H, m), 1.90-1.85 (2H, m), 1.73 (1H, *J*= 12.5 Hz, 1.67-1.59 (1H, m). δ_C 169.5, 143.8, 137.6, 128.7, 128.4, 128.2, 127.7, 127.5, 127.3, 126.9, 126.3, 125.6, 123.9, 107.9, 79.0, 71.0, 63.3, 47.4, 37.9, 36.5, 36.4, 30.9, 23.3. HRMS (ESI) *m/z* calcd for $C_{24}H_{26}NO_2$ $[M + H]^+$ 360.1983, found 360.1986. **19**: $[\alpha]_D^{25}$ + 20.1 (*c* 0.1 $CHCl_3$). ν_{max}/cm^{-1} 2932, 1647, 1417, 1338, 1091, 743, 618. δ_H 7.40-7.31 (10H, m), 6.21 (1H, s), 4.63 (1H, d, *J* = 12.0 Hz), 4.49 (1H, d, *J* = 12.0 Hz), 4.02 (1H, d, *J* = 12.5 Hz), 3.88 (1H, t, *J* = 4.5 Hz), 2.95 (1H, t, *J* = 12.5 Hz), 2.89 (1H, s), 2.76-2.68 (2H, m), 2.50-2.44 (2H, m), 1.97 (1H, d, *J* = 13.0 Hz), 1.85 (1H, d, *J* = 13.0 Hz), 1.71 (1H, *J* = 12.5 Hz), 1.57 (1H, t, *J* = 12.5 Hz). δ_C 170.5, 140.0, 137.7, 137.0, 128.8, 128.4, 127.8, 127.5, 127.4, 126.4, 125.3, 125.0, 79.1, 71.9, 39.6, 36.4, 35.0, 30.6, 29.8, 27.9. LRMS (ESI) *m/z* ($[M + H]^+$) 360.

(1S,7R,9R,10aS)-1-(Benzyloxy)-9-(chloromethyl)-1,2,7,8,9,10-hexahydro-3H-7,10a-methanopyrrolo[1,2-a]azocin-3-one ***(7c)*** *and (1S,7S,9S,10aR)-1-(benzyloxy)-9-(chloromethyl)-1,2,7,8,9,10-hexahydro-3H-7,10a-methanopyrrolo[1,2-a]azocin-3-one* ***(8c).*** The title compounds were prepared in a similar fashion to **5a**/**6a** above, from **3a** (0.050 g, 0.23 mmol), (2-(chloromethyl)allyl)trimethylsilane (0.032 g, 0.28 mmol), toluene (2 mL) and BF_3•Et_2O (0.066 g, 0.47 mmol). The reaction mixture was heated at 70 ^oC for 18 h. Column chromatography (1:1.5 EtOAc/petrol) of the crude product gave a 1:1 mixture of the title compounds (0.038 g, 70%) as a colorless oil. A small amount of each isomer could be obtained in pure form by further separation by column chromatography. **7c**: $[\alpha]_D^{25}$ - 13.4 (*c* 0.2 $CHCl_3$). ν_{max}/cm^{-1} 2954, 1680, 1367, 1033, 1014, 704. δ_H 7.38 – 7.24 (5H, m), 7.01 (1H, d, *J* = 7.0 Hz), 5.12 (1H, t, *J* = 7.0 Hz), 4.60 (1H, d, *J* = 12.0 Hz), 4.44 (1H, d, *J* = 12.0 Hz),

3.77 (1H, d, *J* = 5.0 Hz), 3.45 (1H, dd, *J* = 10.5, 5.5 Hz), 3.38 (1H, dd, *J* = 10.5, 5.5 Hz), 2.77 (1H, dd, *J* = 17.0, 5.0 Hz), 2.69 (1H, br. s), 2.50 (1H, d, *J* = 17.0 Hz), 2.11 (2H, m), 1.82 (1H, d, *J* = 12.5 Hz), 1.73 (1H, d, *J* = 12.5 Hz), 1.63 (1H, d, *J* = 12.5 Hz), 1.44 (1H, td, *J* = 12.5, 3.0 Hz), 1.32 (1H, t, *J* = 12.0 Hz). δ_C 169.5, 137.7, 128.6, 127.9, 127.5, 123.4, 111.2, 79.1, 71.3, 64.1, 50.2 (*C*H_2Cl), 41.4, 36.4, 34.9, 32.6, 29.6, 29.2. LRMS (ESI) *m/z* $[M + H]^+$ 332 (^{35}Cl, 100%), 334 (^{37}Cl, 30%). **8c**: $[\alpha]_D^{25}$ + 94.2 (*c* 0.8 $CHCl_3$). ν_{max}/cm^{-1} 2922, 1706, 1352, 1028, 1004, 642. δ_H (300 MHz) 7.44 – 7.25 (5H, m), 7.00 (1H, d, *J* = 8.0 Hz), 5.11 (1H, t, *J* = 7.1 Hz), 4.60 (2H, q, *J* = 11.9 Hz), 3.87 (1H, t, *J* = 9.0 Hz), 3.45 (2H, d, *J* = 5.8 Hz), 2.58 (3H, m), 2.17 – 2.02 (1H, m), 1.98 (1H, d, *J* = 12.0 Hz), 1.93 (1H, d, *J* = 12.0 Hz), 1.78 (1H, d, *J* = 12.0 Hz), 1.59 (1H, t, *J* = 12.0 Hz), 1.45 (1H, d, *J* = 12.0 Hz), 1.36 (1H, dd, *J* = 12.0, 3.5 Hz). δ_C (75 MHz, $CDCl_3$) 167.8, 137.5, 128.7, 128.2, 127.7, 122.7, 111.4, 80.4, 72.5, 61.7, 50.4, 35.7, 35.1, 34.7, 32.8, 29.3. HRMS (ESI) *m/z* calcd for $C_{19}H_{23}NO_2{}^{35}Cl$ $[M + H]^+$ 332.1412, found 332.1417.

(1S,8R,11aS)-1-(Benzyloxy)-2,3,8,9,10,11-hexahydro-8,11a-methanopyrido[1,2-a]azocin-4(1H)-one ***(17a)*** *and (1S,8R,11aS)-1-(benzyloxy)-2,3,8,9,10,11-hexahydro-8,11a-methanopyrido[1,2-a]azocin-4(1H)-one* ***(18a).*** The title compounds were prepared in a similar fashion to **5a**/**6a** above, from **3c** (0.045 g, 0.0.16 mmol), CH_2Cl_2 (4 mL) allyltrimethylsilane (0.022 g, 0.19 mmol) and BF_3•Et_2O (0.046 g, 0.32 mmol) The crude product was purified by column chromatography (1:1.5 EtOAc/petrol) yielding a 1:1 mixture of the title compounds (0.042 g, 85%) as a colorless oil. A small amount of each isomer could be obtained in pure form by further separation by column chromatography. **17a**: $[\alpha]_D^{25}$ -11.3 (*c* 6.3 $CHCl_3$). ν_{max}/cm^{-1} 2930, 1685, 1639, 1408, 1374, 1066, 739, 692. δ_H 7.57 (1H, d, *J* = 7.5 Hz), 7.44-7.33 (5H, m), 5.07 (1H, t, *J* = 7.5 Hz), 4.70 (1H, d, *J* = 12.0 Hz), 4.48 (1H, d, *J* = 12.0 Hz), 3.40 (1H, s), 2.72 – 2.63 (1H, m), 2.56 – 2.48 (2H, m), 2.39 (1H, d, *J* = 12.8 Hz), 2.11 – 2.02 (2H, d, *J* = 7.5 Hz), 1.86 (1H, d, *J* = 13.0 Hz), 1.70 (1H, dt, *J* = 13.0, 12.0 Hz),

1.56 (2H, d, *J* = 12.0 Hz), 1.47 (1H, dt, *J* = 13.0, 12.0 Hz), 1.36 (1H, d, *J* = 11.0 Hz), 1.31 (1H, d, *J* = 13.0 Hz). $^{13}\delta_C$ 167.2, 138.0, 129.4, 128.4, 128.0, 125.7, 111.0, 77.4, 70.8, 58.6 (C11a), 38.2, 32.9, 28.7, 27.7, 27.0, 18.8, 18.0. HRMS (ESI) *m/z* calcd for $C_{19}H_{24}NO_2$ $[M + H]^+$ 298.1763, found 298.1767. Key NOESY correlation: H1 (3.40 ppm) to H11 (1.36 ppm). **18a**: $[\alpha]_D^{25}$ + 73.8 (*c* 0.5 $CHCl_3$). ν_{max}/cm^{-1} 2922, 1663, 1407, 1331, 1090, 989, 759. δ_H 7.44 (1H, d, *J* = 7.5 Hz), 7.40 – 7.28 (5H, m), 5.09 (1H, t, *J* = 7.5 Hz), 4.66 (1H, d, *J* = 12.5 Hz), 4.54 (1H, d, *J* = 12.5 Hz), 3.38 (1H, dd, *J* = 12.0, 4.6 Hz), 2.65 (1H, dd, *J* = 18.8, 8.3 Hz), 2.57-2.49 (3H, m), 2.19 (1H, d, *J* = 12.0 Hz), 2.12 – 2.02 (1H, m), 1.96 – 1.85 (1H, m), 1.84-1.79 (1H, m), 1.71 (1H, d, *J* = 12.0 Hz), 1.67 – 1.56 (2H, m, 10), 1.52 (2H, br. s), 1.41 (1H, d, *J* = 12.0 Hz). δ_C 166.8, 138.3, 128.7, 127.9, 127.6, 125.6, 111.9, 79.5, 71.8, 58.3 (C11a), 34.9, 31.6, 29.3, 29.0, 28.0, 20.4, 17.9. HRMS (ESI) *m/z* calcd for $C_{19}H_{24}NO_2$ $[M + H]^+$ 298.1763, found 298.1769.

(1S,8R,10R,11aS)-1-(Benzyloxy)-10-methyl-2,3,8,9,10,11-hexahydro-8,11a-methanopyrido[1,2-a]azocin-4(1H)-one ***(17b)*** *and (1S,8S,10S,11aR)-1-(benzyloxy)-10-methyl-2,3,8,9,10,11-hexahydro-8,11a-methanopyrido[1,2-a]azocin-4(1H)-one* ***(18b)***

The title compounds were prepared in a similar fashion to **5a**/**6a** above, from **3c** (0.045 g, 0.16 mmol), metallyltrimethylsilane (0.025 g, 0.19 mmol), CH_2Cl_2 (4 mL) and BF_3•Et_2O (0.046 g, 0.32 mmol). Column chromatography (1:1.5 EtOAc/petrol) of the crude product gave a 1:1 mixture of the title compounds (0.041 g, 83%) as a colorless oil. A small amount of isomer **18b** could be obtained in pure form by further separation by column chromatography. **18b**: $[\alpha]_D^{25}$ + 62.7 (*c* 0.1 $CHCl_3$). ν_{max}/cm^{-1} 2928, 1676, 1412, 1354, 1079, 765, 693. δ_H 7.33 (6H, m), 5.14 (1H, t, *J* = 7.5 Hz), 4.68 (1H, d, *J* = 12.0 Hz), 4.51 (1H, d, *J* = 12.0 Hz), 3.41 (1H, dd, *J* = 12.0, 3.5 Hz), 2.66 (1H, dd, *J* = 18.5, 8.5 Hz), 2.54 – 2.50 (1H, m), 2.46 (1H, m), 2.13 (1H, d, *J* = 12.0 Hz), 2.08 (1H, m), 1.94 (1H, m), 1.83 (1H, m), 1.72

(1H, t, *J* = 13.0 Hz), 1.59 (1H, d, *J* = 13.0 Hz), 1.43 (1H, d, *J* = 13.0 Hz), 1.14 (2H, m), 0.89 (3H, d, *J* = 6.0 Hz). δ_C 166.6, 137.5, 128.4, 127.8, 127.7, 124.9, 112.4, 79.3, 71.6, 59.2 (C11a), 40.1, 37.9, 34.4, 29.1, 28.0, 24.1, 21.8, 20.1. HRMS (ESI) *m/z* calcd for $C_{20}H_{26}NO_2$ $[M + H]^+$ 312.1954, found 312.1956. **17b**: (in part from ^{1}H NMR spectrum of the mixture) δ_H 7.47 (1H, d, *J* = 8.0 Hz), 5.08 (1H, t, *J* = 8.0 Hz), 4.45 (1H, d, *J* = 11.9 Hz), 3.37 (1H, s), 0.86 (3H, d, *J* = 6.3 Hz).

(1S,8R,10R,11aS)-1-(Benzyloxy)-10-phenyl-2,3,8,9,10,11-hexahydro-8,11a-methanopyrido[1,2-a]azocin-4(1H)-one ***(17c)*** *and (1S,8S,10S,11aR)-1-(benzyloxy)-10-phenyl-2,3,8,9,10,11-hexahydro-8,11a-methanopyrido[1,2-a]azocin-4(1H)-one* ***(18c).*** The title compounds were prepared in a similar fashion to **5a**/**6a** above, from **3c** (0.050 g, 0.18 mmol), trimethyl(2-phenylallyl)silane[11] (0.063 g, 0.18 mmol), CH_2Cl_2 (2 mL) and BF_3•Et_2O (0.051 g, 0.36 mmol). Column chromatography (1:1.5 EtOAc/petrol) of the crude product gave a 7:3 mixture of the title compounds (0.039 g, 58%), respectively, as a colorless oil. A small amount of **17c** could be obtained pure by further column chromatography. **17c**: $[\alpha]_D^{25}$ -2.3 (*c* 0.1 $CHCl_3$). ν_{max}/cm^{-1} 2941, 1678, 1396, 1299, 1103, 761, 687. δ_H 7.51 (1H, d, *J* = 8.0 Hz), 7.40 – 7.15 (10H, m), 5.22 (1H, t, *J* = 8.0 Hz), 4.69 (1H, d, *J* = 11.9 Hz), 4.53 (1H, d, *J* = 11.9 Hz), 3.44 (1H, s), 3.10 – 2.99 (1H, m), 2.65 (2H, m), 2.49 (2H, m), 2.07 – 1.97 (2H, m), 1.93 – 1.86 (1H, m), 1.78 (1H, d, *J* = 13.5 Hz), 1.74 – 1.66 (1H, m), 1.54 – 1.42 (2H, m). δ_C 166.8, 145.8, 138.1, 128.6, 128.6, 128.5, 128.0, 127.8, 127.4, 126.4, 112.2, 79.1, 71.8, 58.9, 47.2, 46.3, 39.5, 36.2, 36.1, 34.5, 20.2. HRMS (ESI) *m/z* 374 $[M + H]^+$. **18c** (in part from ^{1}H NMR spectrum of the mixture) δ_H 7.61 (1H, d, *J* = 8.0 Hz), 5.17 (1H, t, *J* = 8.0 Hz), 3.46 (1H, dd, *J* = 4.7, 11.8 Hz).

Deuterium Labelling Studies

(S)-1-(But-3-en-1-yl-1,1-d_2)-2,5-dioxopyrrolidin-3-yl acetate. The title compound was prepared in an analogous fashion to its non-deuterated analogue as described earlier.[5] *L*-Malic acid (0.626 g, 4.671 mmol) was heated at reflux in acetyl chloride (40 mL) for 2 h then the excess amount of acetyl chloride was evaporated *in vacuo* to give a colorless oil. A solution of this oil in CH_2Cl_2 (10 mL) was treated with a solution of but-3-en-1,1-d_2-1amine[12] (0.341 g, 4.671 mmol) in CH_2Cl_2 (10 mL) at 0 ^oC. The resulting solution was stirred at ambient temperature for 16 h. The CH_2Cl_2 was evaporated *in vacuo* to afford a white solid which was then heated at reflux with acetyl chloride (40 mL) for 3 h. After evaporation of the excess amount of acetyl chloride the crude product was subjected to column chromatography (1:1, EtOAc/petrol) to yield the desired product (0.253 g, 41%) as a light yellow oil. $[\alpha]_D^{25}$ - 17.3 (*c* 0.4 $CHCl_3$). ν_{max}/cm^{-1} 3453, 1746, 1679, 1387, 1352, 1191, 1112, 923. δ_H (300 MHz) 5.77-5.68 (1H, m), 5.43 (1H, dd, *J* = 5.0, 8.5 Hz), 5.09-5.04 (2H, m), 3.15 (1H, dd, *J* = 8.5, 18.0 Hz), 2.64 (1H, dd, *J* = 5.0, 18.0 Hz), 2.36 (2H, d, *J* = 6.9 Hz), 2.16 (3H, s). δ_C (75 MHz, $CDCl_3$) 173.3, 173.1 , 169.7 , 133.8 , 117.6 , 67.2, 37.5 (N*C*D_2, quintet, *J* = 21.7 Hz), 35.1, 31.3, 20.3. LRMS (ESI) *m/z* $[M + H]^+$ 214.

(S)-1-(But-3-en-1-yl-1,1-d_2)-3-hydroxypyrrolidine-2,5-dione. The title compound was prepared in an analogous fashion to its non-deuterated analogue as described earlier.[5] (*S*)-1-(But-3-en-1-yl-1,1-d_2)-2,5-dioxopyrrolidin-3-yl acetate (0.238 g, 1.11 mmol) was dissolved in EtOH (20 mL) and treated with acetyl chloride (0.325 g, 4.17 mmol) at ambient temperature for 16 h. The EtOH was evaporated and the crude product was subject to column chromatography (1:1, EtOAc/petrol) to afford the desired product (0.142 g) as a colorless oil in 75% yield. $[\alpha]_D^{25}$ - 72.0 (*c* 0.3 $CHCl_3$). ν_{max}/cm^{-1} 3443, 1689, 1389, 1342, 1175, 1122, 921. δ_H 5.73-5.66 (1H, m), 5.07-5.03 (2H, m), 4.66 (1H, dd, *J* = 5.0, 8.0 Hz), 4.41 (1H, s, OH), 3.07 (1H, dd, *J* = 8.0, 18.0 Hz), 2.67 (1H, dd, *J* = 5.0, 18.0 Hz), 2.33 (2H, d, *J* = 6.5 Hz). δ_C

178.6, 174.2, 133.8, 117.6, 66.6, 37.3 (NCD_2, quintet, J = 21.0 Hz), 37.0, 31.4. LRMS (ESI) *m/z* $[M + H]^+$ 172.

(S)-3-(Benzyloxy)-1-(but-3-en-1-yl-1,1-d$_2$)pyrrolidine-2,5-dione. The title compound was prepared in an analogous fashion to its non-deuterated analogue as described earlier[5] in a similar manner to **9c** described above from (*S*)-1-(but-3-en-1-yl-1,1-d_2)-3-hydroxypyrrolidine-2,5-dione (0.130 g, 0.75 mmol), Et_2O (10 mL) BnBr (0.258 g, 1.51 mmol) and Ag_2O (0.350 g, 1.51 mmol). Column chromatography (1:4, EtOAc/petrol) of the crude product gave the desired compound (0.195 g) in 90% yield as a colorless oil. $[\alpha]_D^{25}$ -65.0 (*c* 4.2 $CHCl_3$). ν_{max}/cm^{-1} 1696, 1405, 1329, 1115, 919. δ_H 7.34-7.28 (5H, m), 5.72-5.67 (1H, m), 5.05-5.00 (2H, m), 4.93 (1H, d, J = 12.0 Hz), 4.73 (1H, d, J = 12.0 Hz), 4.29 (1H, dd, J = 4.5, 8.5 Hz), 2.86 (1H, dd, J = 8.5, 18.0 Hz), 2.59 (1H, dd, J = 4.5, 18.0 Hz), 2.31 (2H, d, J = 6.5 Hz). δ_C 175.8, 174.1, 136.8, 134.1, 128.5, 128.2, 128.1, 117.6, 72.8, 72.1, 36.9 (NCD_2, quintet, J = 20.8 Hz), 36.1, 31.6. LRMS (ESI) *m/z* $[M + H]^+$ 262.

(4S,5S)-4-(Benzyloxy)-1-(but-3-en-1-yl-1,1-d$_2$)-5-hydroxy-5-vinylpyrrolidin-2-one. The title compound was prepared in an analogous fashion to its non-deuterated analogue as described earlier[5] in a similar manner to **10b** described above from (*S*)-3-(benzyloxy)-1-(but-3-en-1-yl-1,1-d_2)pyrrolidine-2,5-dione (0.289 g, 0.34 mmol), THF (5 mL) and vinylmagnesium bromide (0.51 mmol, 1M solution in THF) at 0 ^oC. After stirring the mixture at 0 ^oC for 1.5 h, the reaction mixture was quenched with NH_4Cl (5 mL, saturated aqueous solution) After a similar work up procedure the crude product was purified by column chromatography (1:1, EtOAc/petrol) yielding the title compound as a colorless oil (74 mg, 76%) and as a mixture of distereomers (20:80). A small amount of each isomer could be obtained in pure form by further separation by column chromatography. Major isomer: $[\alpha]_D^{25}$ + 45.1 (*c* 0.9 $CHCl_3$). ν_{max}/cm^{-1} 3290, 2941, 1670, 1409, 1360, 1077, 919, 738. δ_H 7.34-7.28 (5H, m), 6.05 (1H, dd,

J = 11.0, 17.5 Hz), 5.80-5.72 (1H, m), 5.60 (1H, d, *J* = 17.0 Hz), 5.47 (1H, d, *J* = 11.0 Hz,), 5.07-5.04 (2H, m), 4.62 (1H, d, *J* = 11.5 Hz), 4.52 (1H, d, *J* = 11.5 Hz), 3.95 (1H, t, *J* = 6.5 Hz), 3.53 (1H, s, OH), 2.75 (1H, dd, *J* = 6.5, 16.5 Hz), 2.38 (1H, dd, *J* = 4.5, 16.5 Hz), 2.30 (2H, d, *J* = 6.5 Hz). δ_C 172.0, 137.1, 135.7, 134.9, 128.1, 127.5, 127.3, 117.8, 116.6, 92.5, 81.6, 71.7, 38.1 (NCD_2, quintet, *J* = 20.0 Hz), 36.1, 32.8. LRMS (ESI) *m/z* $[M + H]^+$ 290. Minor isomer: $[\alpha]_D^{25}$ + 51.9 (*c* 1.8 $CHCl_3$). ν_{max}/cm^{-1} 3290, 1663, 1418, 1357, 1076, 916, 731. δ_H 7.37-7.29 (5H, m), 5.78-5.73 (2H, m), 5.51 (1H, d, *J* = 17.0 Hz), 5.36 (1H, d, *J* = 10.5 Hz), 5.04 (1H, d, *J* = 17.5 Hz), 4.99 (1H, d, *J* = 10.0 Hz), 4.63 (1H, d, *J* = 11.5 Hz), 4.59 (1H, d, *J* = 11.5 Hz), 3.89 (1H, t, *J* = 6.0 Hz), 3.85 (1H, s, OH), 2.57 (1H, dd, *J* = 6.0, 16.5 Hz), 2.48 (1H, dd, *J* = 2.5, 16.5 Hz), 2.33 (2H, d, *J* = 6.5 Hz,). δ_C 171.4, 137.2, 136.5, 135.5, 128.6, 128.3, 127.8, 118.2, 116.4, 90.2, 77.0, 72.4, 38.8 (NCD_2, quintet, *J* = 20.0 Hz), 35.4, 33.2 ($CH_2CH{=}CH_2$). LRMS (ESI) *m/z* $[M + H]^+$ 290.

(1S,8aS)-1-(Benzyloxy)-8a-hydroxy-1,5,6,8a-tetrahyroindolizin-3(2H)-one-5,5-d_2 ***(20).*** The title compound was prepared in a similar manner to its non-deuterated analogue **3a** as described above from (4*S*,5*S*)-4-(benzyloxy)-1-(but-3-en-1-yl-1,1-d_2)-5-hydroxy-5-vinylpyrrolidin-2-one (0.020 g, 0.06 mmol), CH_2Cl_2 (2 mL) and Grubbs' 1st generation catalyst (0.003 g, $3.46x10^{-3}$ mmol). After 1 h the CH_2Cl_2 was evaporated *in vaccuo*. The crude product was purified by column chromatography (2:1 EtOAc/petrol) yielding the title compound (0.015 g, 87%) as a pale yellow oil. δ_H 7.29 – 7.18 (5H, m), 5.98 – 5.91 (1H, m), 5.85 (1H, d, *J* = 10.0 Hz), 4.51 (1H, d, *J* = 12.0 Hz), 4.44 (1H, d, *J* = 12.1 Hz), 3.97 (1H, d, *J* = 5.0 Hz), 2.76 (1H, dd, *J* = 17.0, 5.0 Hz), 2.30 (d, *J* = 17.0 Hz), 2.17 (1H, d, *J* = 17.5 Hz), 1.97 (dd, *J* = 17.5, 5.5 Hz).

(1S,7R,9R,10aS)-1-(Benzyloxy)-9-methyl-1,2,7,8,9,10-hexahydro-3H-7,10a-methanopyrrolo[1,2-a]azocin-3-one-5,9-d_2 ***(26)*** *and (1S,7S,9S,10aR)-1-(benzyloxy)-9-methyl-*

*1,2,7,8,9,10-hexahydro-3H-7,10a-methanopyrrolo[1,2-a]azocin-3-one-5,9-d_2 (**27**).* The title compounds were prepared in a similar manner to their non-deuterated analogues **7a**/**8a** described above from **20** (0.020 g, 0.07 mmol), methallyltrimethylsilane (0.011 g, 0.09 mmol), CH_2Cl_2 (2 mL) and BF_3•Et_2O (0.021 g, 0.15 mmol). Column chromatography (1:1 EtOAc/petrol) gave a 1:1 mixture the title compounds (0.017 g, 75%) as a colorless oil. A small amount of each isomer could be obtained in pure form by further separation by column chromatography. **26**: $[\alpha]_D^{25}$ - 19.9 (*c* 0.3 $CHCl_3$). ν_{max}/cm^{-1} 2929, 1686, 1627, 1405, 1381, 1072, 738, 697. δ_H 7.35-7.26 (5H, m), 5.10 (1H, d, *J* = 6.0 Hz), 4.59 (1H, d, *J* = 12.0 Hz), 4.42 (1H, d, *J* = 12.0 Hz), 3.72 (1H, d, *J* = 5.0 Hz), 2.75 (1H, dd, *J* = 5.0, 17.0 Hz), 2.60 (1H, br. s), 2.46 (1H, d, *J* = 17.0 Hz), 2.09 (1H, d, *J* = 12.5 Hz), 1.71-1.58 (3H, m), 1.19 (1H, d, *J* = 11.5 Hz), 1.09 (1H, d, *J* = 11.5 Hz), 0.84 (3H, s, Me). δ_C 169.3, 137.8, 128.4, 127.7, 127.3, 123.0 (t, *J* = 26.8 Hz), 111.5, 79.2, 71.1, 64.4, 46.1, 39.2, 36.3, 29.7, 29.5, 24.5 (t, *J* = 19.3 Hz), 21.6. LRMS (ESI) *m/z* $[M + H]^+$ 300. **27**: $[\alpha]_D^{25}$ + 44.1 (*c* 0.2 $CHCl_3$). ν_{max}/cm^{-1} 2921, 1696, 1622, 1390, 1084, 741, 687.δ_H 7.38-7.26 (5H, m), 5.09 (1H, d, *J* = 6.5 Hz), 4.61 (1H, d, *J* = 12.0 Hz), 4.57 (1H, d, *J* = 12.0 Hz), 3.89 (1H, t, *J* = 9.0 Hz), 2.56 (2H, d, *J* = 9.0 Hz), 2.52 (1H, br. s), 1.95 (1H, d, *J* = 11.5 Hz), 1.79 (1H, d, *J* = 13.5 Hz), 1.62 (1H, br. s), 1.39 (2H, m), 1.18 (1H, d, *J* = 13.0 Hz), 0.90 (3H, s). δ_C (125 MHz, $CDCl_3$) 167.7, 137.6, 128.5, 127.9, 127.5, 122.0 (t, *J* = 27.7 Hz), 111.78, 80.6, 72.3, 62.0, 39.9, 38.9, 35.6, 35.2, 29.8, 24.2 (t, *J* = 19.5 Hz), 21.6. LRMS (ESI) *m/z* $[M + H]^+$ 300.

Reactions of pyrrolo[1,2-*a*]azepines 3e and 13-15

*(1S,8R,9aR)-8,9a-Diallyl-1-(benzyloxy)octahydro-3H-pyrrolo[1,2-a]azepin-3-one (**28**).* The title compound was prepared in a similar fashion to **5a**/**6a** above, from **3e** (0.075 g, 0.27 mmol), allyltrimetylsilane (0.047 g, 0.41 mmol), CH_2Cl_2 (5 mL) and BF_3•Et_2O (0.058 g, 0.41 mmol). The crude product was purified by column chromatography (1:2 EtOAc/petrol)

yielding the title compound (0.031 g, 34%) as a colourless oil. $[\alpha]_D^{25}$ + 63.9 (*c* 0.2 $CHCl_3$). ν_{max}/cm^{-1} 2922, 1717, 1665, 1470, 1072, 734, 690. δ_H 7.41 – 7.29 (5H, m), 5.92 (1H, m), 5.66 – 5.56 (1H, m), 5.07 (1H, d, *J* = 9.0 Hz), 5.01 (3H, m), 4.64 (1H, d, *J* = 12.0 Hz), 4.46 (1H, d, *J* = 12.0 Hz), 4.02 (1H, d, *J* = 13.5 Hz), 3.88 (1H, t, *J* = 9.0 Hz), 2.59 (1H, t, *J* = 13.5 Hz), 2.55 – 2.40 (3H, m, C*H*$_2$CH=CH_2), 2.21 (1H, dd, *J* = 14.0, 8.0 Hz), 2.00 – 1.93 (1H, m), 1.90 (1H, d, *J* = 14.0 Hz), 1.86 (1H, dd, *J* = 14.0, 7.0 Hz), 1.79 – 1.73 (1H, m), 1.66 (1H, dd, *J* = 14.0, 2.0 Hz), 1.46 – 1.40 (1H, m), 1.39 – 1.27 (2H, m), 1.06 (1H, m). δ_C 171.1, 136.7, 133.9, 128.6, 128.0, 127.8, 127.7, 119.1, 116.9, 77.1, 72.4, 67.0, 43.5, 42.5, 39.9, 39.5, 37.3, 36.5, 34.2, 28.5. HRMS (ESI) *m/z* calcd for $C_{22}H_{30}NO_2$ $[M + H]^+$ 340.2213, found 340.2216. Key NOESY correlation between H1 (3.88 ppm) and H9 (1.90 ppm)

*2-((Trimethylsilyl)methyl)-2,3,9,10-tetrahydro-7H-furo[3,2-d]pyrrolo[1,2-a]azepin-7-one (**29**).* The title compound was prepared in a similar fashion to **5a**/**6a** above, from **13** (0.070 g, 0.24 mmol), allyltrimethylsilane (0.033 g, 0.29 mmol), CH_2Cl_2 (5 mL) and BF_3•Et_2O (0.067 g, 0.48 mmol). Column chromatography (1:4 EtOAc/petrol) of the crude product gave the title compound (0.033 g, 51%) as a bright yellow oil. ν_{max}/cm^{-1} 2930, 1657, 1362, 1219, 748, 693. δ_H (300 MHz) 6.87 (1H, d, *J* = 5.5 Hz), 6.01 (1H, d, *J* = 5.5 Hz), 5.57 (1H, s), 4.84 – 4.73 (1H, m), 3.98 – 3.82 (2H, m), 2.96 (1H, dd, *J* = 13.5, 9.5 Hz), 2.63 (2H, s), 2.47 (1H, dd, *J* = 13.5, 8.0 Hz), 1.28 – 1.17 (1H, dd, *J* = 14.0, 7.5 Hz), 1.05 (1H, dd, *J* = 14.0, 8.5 Hz), 0.07 (9H, s). δ_C 170.5, 160.7, 137.1, 136.7, 119.3, 110.1, 106.3, 81.6, 41.0, 37.2, 28.6, 25.4, 0.9. HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NO_2Si$ $[M + H]^+$ 276.1316, found 276.1319.

*2,2-Dimethyl-2,3,9,10-tetrahydro-7H-furo[3,2-d]pyrrolo[1,2-a]azepin-7-one (**30**).* The title compound was prepared in a similar fashion to **5a**/**6a** above, from **13** (0.070 g, 0.24 mmol), methallyltrimethylsilane (0.037 g, 0.29 mmol), CH_2Cl_2 (5 mL) and BF_3•Et_2O (0.067 g, 0.48 mmol). Column chromatography (1:3 EtOAc/petrol) of the crude product gave the title

compound (0.023 g, 45%) as a bright yellow oil. ν_{max}/cm^{-1} 2971, 1652, 1618, 1452, 1337, 1264, 1190, 747. δ_H 6.87 (1H, d, *J* = 5.5 Hz), 6.02 (1H, d, *J* = 5.5 Hz), 5.55 (1H, s), 3.95 – 3.87 (2H, m), 2.72 – 2.64 (2H, br s), 2.63 (2H, dd, *J* = 7.0, 3.0 Hz), 1.40 (6H, s). δ_C 170.6, 160.0, 137.3, 136.8, 119.5, 110.4, 106.0, 86.2, 45.8, 38.6, 29.0, 28.4. HRMS (ESI) *m/z* calcd for $C_{13}H_{16}NO_2$ $[M + H]^+$ 218.1156, found 218.1160.

(2R,3aS,5S,10aR)-5-(Benzyloxy)-2-((trimethylsilyl)methyl)-2,3,3a,5,6,9,10,10a-octahydro-7H-furo[3,2-d]pyrrolo[1,2-a]azepin-7-one ***(31).*** The title compound was prepared in a similar fashion to **5a**/**6a** above from **15** (0.060 g, 0.20 mmol) and allyltrimetylsilane (0.071 g, 0.62 mmol), CH_2Cl_2 (2 mL) and BF_3•Et_2O (0.056 g, 0.40 mmol). The crude product was purified by column chromatography (1:3 EtOAc/petrol) yielding the title compound (0.036 g, 47%) as a colorless oil. $[\alpha]_D^{25}$ + 11.6 (*c* 0.2 $CHCl_3$). ν_{max}/cm^{-1} 2923, 1715, 1671, 1430, 1338, 1219, 912, 693. δ_H 7.33 (5H, m), 4.81 (1H, d, *J* = 5.0 Hz), 4.55 (2H, s), 4.35 (1H, d, *J* = 7.0 Hz), 4.10 (1H, t, *J* = 8.5 Hz), 4.03 – 3.92 (1H, m), 3.92 – 3.83 (1H, m), 3.26 (1H, m), 3.17 – 3.03 (1H, m), 2.62 (1H, dd, *J* = 17.0, 7.0 Hz), 2.49 (1H, d, *J* = 17.0 Hz), 2.28 (1H, dd, *J* = 12.0, 7.4 Hz), 2.07 – 1.92 (1H, m), 1.91 – 1.78 (1H, m), 1.34 (1H, m), 1.09 (1H, dd, *J* = 14.0, 5.5 Hz), 0.81 (1H, dd, *J* = 14.0, 9.0 Hz), 0.06 – -0.07 (9H, s). δ_C 170.5, 137.1, 136.2, 128.4, 127.5, 126.9, 106.9, 81.4, 76.7, 75.3, 71.2, 45.3, 41.0, 37.8, 37.4, 29.6, 24.5, -0.93. HRMS (ESI) *m/z* calcd for $C_{22}H_{32}NO_3Si$ $[M + H]^+$ 386.2148, found 386.2144. Key NOESY correlations between H3a (3.17-3.03 ppm) and H10a (4.10 ppm) and H2 (3.92-3.83 ppm).

(1S,7S,9aR)-1-(Benzyloxy)-1,2,6,7-tetrahydro-3H,5H-7,9a-epoxypyrrolo[1,2-a]azepin-3-one ***(32).*** The title compound was prepared in a similar fashion to **5a**/**6a** above from **14** (0.050 g, 0.17 mmol), allyltrimetylsilane (0.059 g, 0.51 mmol), CH_2Cl_2 (2 mL) and BF_3•Et_2O (0.048 g, 0.34 mmol) at 0 ^oC. The resulting reaction mixture was stirred at 0 ^oC for 30 min. The crude product was purified by column chromatography (1:1 EtOAc/petrol) yielding the title

compound (0.037 g, 80%) as a colorless oil. $[\alpha]_D^{25}$ + 21.6 (*c* 0.1 $CHCl_3$). ν_{max}/cm^{-1} 2925 1717, 1675, 1338, 1219, 907, 698. δ_H 7.38 – 7.27 (5H, m), 6.53 (1H, d, *J* = 5.8 Hz), 6.35 (1H, d, *J* = 5.8 Hz), 4.88 (1H, s), 4.64 (1H, d, *J* = 11.7 Hz), 4.55 (1H, d, *J* = 11.7 Hz), 4.26 (1H, dd, *J* = 8.0, 5.0 Hz), 3.94 (1H, dd, *J* = 13.0, 7.1 Hz), 3.07 (1H, td, *J* = 13.0, 5.5 Hz), 2.80 (1H, dd, *J* = 17.5, 8.0 Hz), 2.47 (1H, dd, *J* = 17.5, 5.0 Hz), 2.12 – 2.04 (1H, m), 1.45 (1H, dd, *J* = 13.0, 5.5 Hz). δ_C 169.5, 137.4, 133.8, 128.6, 128.0, 127.8, 127.6, 102.4, 79.4, 76.0, 72.4, 37.0, 34.1, 24.7. HRMS (ESI) *m/z* calcd for $C_{16}H_{18}NO_3$ $[M + H]^+$ 272.1287, found 272.1275. Key NOESY correlation between H9 (6.35 ppm) and CH_2Ph (4.64 ppm).

*(1S,7R,8S,9aS)-8-Allyl-1-(benzyloxy)hexahydro-3H,5H-7,9a-epoxypyrrolo[1,2-a]azepin-3-one (**33**).* **Method A:** The title compound was prepared in a similar fashion to **5a**/**6a** above from **32** (0.020 g, 0.07 mmol), allyltrimethylsilane (0.014 g, 0.11 mmol), CH_2Cl_2 (1 mL) and BF_3•Et_2O (0.015 g, 0.11 mmol). The crude product was purified by column chromatography (1:2 EtOAc/petrol) yielding the title compound (0.016 g, 75%) as a colorless oil. **Method B:** To a solution of **14** (0.050 g, 0.17 mmol) and allyltrimethylsilane (0.059 g, 0.51 mmol) in CH_2Cl_2 (2 mL) was added $BF_3{\cdot}Et_2O$ (0.048 g, 0.34 mmol) dropwise at 0 ^oC. The resulting mixture was stirred at 0 ^oC for 2 h and then at rt for 3 h. The crude product was purified by column chromatography (1:2 EtOAc/petrol) yielding the title compound (0.040 g, 76%) as a colorless oil. $[\alpha]_D^{25}$ + 61.6 (*c* 0.4 $CHCl_3$). ν_{max}/cm^{-1} 2923, 1715, 1671, 1430, 1338, 1219, 912, 693. δ_H 7.41 – 7.28 (5H, m), 5.87 – 5.73 (1H, m), 5.14 – 5.02 (2H, m), 4.60 (2H, s), 4.42 – 4.35 (1H, m), 4.12 (1H, dd, *J* = 7.5, 4.5 Hz), 4.01 (1H, dd, *J* = 13.0, 7.5 Hz), 3.11 (1H, td, *J* = 13.0, 5.0 Hz), 2.73 (3H, m), 2.62 – 2.53 (1H, m), 2.43 (1H, dd, *J* = 17.0, 4.5 Hz), 2.33 – 2.26 (2H, m), 1.93 (1H, m), 1.63 – 1.54 (2H, m). δ_C 170.1, 137.4, 136.7, 128.6, 128.1, 127.8, 116.3 , 99.5, 78.0, 77.4, 76.4, 39.5, 36.7, 35.2, 34.5, 33.5, 23.7. LRMS (ESI) *m/z* 314 $[M + H]^+$. Key NOESY correlation between H7 (4.42-4.35 ppm) and H8 (2.62-2.53 ppm).

Synthesis of compounds 41–44.

(1S,7R)-1-(Benzyloxy)-7-(propa-1,2-dien-1-yl)-1,5,6,7-tetrahydroindolizin-3(2H)-one ***(41).*** The title compound was prepared in a similar fashion to **5a**/**6a** above from **33** (0.124 g, 0.47 mmol), trimethylpropargylsilane (0.064 g, 0.57 mmol), CH_2Cl_2 (5 mL) and BF_3•Et_2O (0.135 g, 0.95 mmol). Column chromatography (1:2 EtOAc/petrol) of the crude product gave the title compound (0.054 g, 42%) as a colorless oil and as a mixture of diastereomers (66:33). A small amount of major isomer could be obtained in pure form by further separation by column chromatography. Major diastereomer: $[\alpha]_D^{25}$ + 94.2 (*c* 0.8 $CHCl_3$). ν_{max}/cm^{-1} 2922, 1957, 1706, 1352, 1028, 1004, 642. δ_H 7.44 – 7.29 (5H, m), 5.20 (1H, dt, *J* = 6.0, 4.5 Hz), 5.09 (1H, s), 4.85 – 4.78 (2H, s), 4.68 (1H, d, *J* = 12.0 Hz), 4.61 – 4.55 (2H, m), 3.63 (1H, dd, *J* = 12.0, 6.0 Hz), 3.55 (1H, m), 3.04 (1H, s), 2.72 (1H, dd, *J* = 17.5, 7.5 Hz), 2.55 (1H, d, *J* = 17.5 Hz), 1.94 – 1.84 (1H, m), 1.81 – 1.72 (1H, m). δ_C 207.4, 171.7, 139.3, 137.5, 128.6, 128.0, 127.9, 104.3, 93.3, 77.1, 71.8, 70.9, 37.4, 36.9, 31.5, 26.6. HRMS (ESI) *m/z* calcd for $C_{18}H_{20}NO_2$ $[M + H]^+$ 282.1517, found 282.1521. Minor isomer (in part from ^{1}H NMR spectrum of the mixture): δ_H 5.28 (1H, t, *J* = 6.5 Hz), 5.01 (1H, s), 4.87 (2H, s), 4.60 (1H, d, *J* = 11.5 Hz).

(1S,7S,10aR)-1-(Benzyloxy)hexahydro-3H-7,10a-metahnopyrrolo[1,2-a]azocine-3,9(10H)-dione ***(42).*** The major diastereomer of **41** (0.021 g, 0.06 mmol) was dissolved in formic acid (0.5 mL) and the solution was heated at 60 ^oC for 5 h. The formic acid was evaporated *in vacuo* then the crude product was dissolved in CH_2Cl_2 (5 mL) which was then washed with a saturated aqueous solution $NaHCO_3$ (3.0 mL), H_2O (3.0 mL) and a saturated aqueous solution of NaCl (3.0 mL). The organic layer was dried over $MgSO_4$, concentrated in *vacuo* and subjected to column chromatography (2:1 EtOAc/petrol) to afford the title product (0.011 g, 57%) as a colorless oil. $[\alpha]_D^{25}$ + 50.3 (*c* 0.1 $CHCl_3$). ν_{max}/cm^{-1} 1714, 1662, 1369, 1070, 1008,

692. δ_H 7.40 – 7.28 (5H, m), 4.64 (1H, d, *J* = 12.0 Hz), 4.46 (1H, d, *J* = 12.0 Hz), 4.07 (1H, dd, *J* = 14.5, 6.0 Hz), 3.77 (1H, t, *J* = 6.5 Hz), 2.68 (3H, m), 2.61 – 2.53 (3H, m), 2.45 (1H, dd, *J* = 17.5, 5.5 Hz), 2.41 (1H, d, *J* = 17.5 Hz), 2.05 (1H, d, *J* = 13.5 Hz), 1.98 (1H, d, *J* = 13.5 Hz), 1.76-1.63 (1H, m), 1.60 (1H, d, *J* = 14.0 Hz). δ_C 208.9, 170.3, 137.5, 128.7, 128.2, 127.7, 78.1, 72.1, 64.6, 51.5, 46.1, 36.1, 34.7, 32.2, 29.9, 29.0. HRMS (ESI) *m/z* calcd for $C_{18}H_{22}NO_3$ $[M + H]^+$ 300.1518, found 300.1517. Key NOESY correlation between H1 (3.77 ppm) and H10 (2.41 ppm)

(1S,7R)-1-(Benzyloxy)-7-(E)-styryl)-1,5,6,7-tetrahydroindolizin-3(2H)-one ***(43).*** The title compound was prepared in a similar fashion to **5a**/**6a** above from **3a** (0.050 g, 0.19 mmol), (*E*)-β-styrylboronic acid (0.034 g, 0.23 mmol), CH_2Cl_2 (3 mL) and BF_3•Et_2O (0.055 g, 0.38 mmol). Column chromatography (1:1 EtOAc/petrol) of the crude product gave the title compound (0.029 g, 45%) as a colorless oil and as a mixture of diastereomers (66:33). A small amount of major isomer could be obtained in pure form by further separation by column chromatography. Major diastereomer: $[\alpha]_D^{25}$ - 14.7 (*c* 1.3 $CHCl_3$). ν_{max}/cm^{-1} 2922, 1683, 1412, 1071, 915, 743. δ_H 7.40 – 7.20 (10H, m), 6.41 (1H, d, *J* = 15.8 Hz), 6.14 (1H, dd, *J* = 15.8, 7.3 Hz), 5.09 (1H, d, *J* = 3.5 Hz), 4.66 – 4.57 (3H, m), 3.66 – 3.51 (2H, m), 3.20 (1H, br. s), 2.72 (1H, dd, *J* = 17.5, 7.5 Hz), 2.55 (dd, *J* = 17.5, 2.5 Hz), 1.99 (1H, m), 1.73 – 1.63 (1H, m). δ_C 171.7, 139.7, 137.5, 137.1, 132.3, 130.6, 128.6, 128.0, 127.9, 127.4, 126.2, 104.0, 71.8, 70.9, 37.4, 36.7, 35.6, 26.8. HRMS (ESI) *m/z* calcd for $C_{23}H_{24}NO_2$ $[M + H]^+$ 346.1769, found 346.1772. Minor isomer (in part from ^{1}H NMR spectrum of the mixture): δ_H 6.50 (1H, d, *J* = 14.6 Hz), 4.98 (1H, s), 4.55 (1H, t, *J* = 6.6 Hz), 3.82-3.76 (2H, m).

(1S,7S,8aR)-1-(Benzyloxy)-7-((E)-styryl)hexahydroindolizin-3(2H)-one ***(44).*** The enamide **43** (0.024 g, 0.06 mmol) was dissolved in AcOH (1 mL) and $NaCNBH_3$ (0.021 g, 0.34 mmol) was added portionwise at rt. The resulting reaction mixture was stirred at rt for 18 h.

Saturated aqueous solution of $NaHCO_3$ (3 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2x2 mL). The combined organic layers was dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (1:2 EtOAc/petrol) yielding the title compound (0.015 g, 75%) as a colorless oil. $[\alpha]_D^{25}$ - 23.1 (*c* 1.4 $CHCl_3$). ν_{max}/cm^{-1} 2923, 1685, 1405, 1181, 932, 704. δ_H 7.39 – 7.20 (10H, m), 6.42 – 6.38 (1H, d, *J* = 16.0 Hz), 6.10 (1H, dd, *J* = 16.0, 7.0 Hz), 4.58 (1H, d, *J* = 11.7 Hz), 4.52 (1H, d, *J* = 11.7 Hz), 4.23 (1H, dd, *J* = 13.0, 3.5 Hz), 3.91 – 3.86 (1H, m), 3.54 (1H, dt, *J* = 13.0, 3.5 Hz), 2.80 – 2.67 (2H, m), 2.50 (1H, dd, *J* = 17.0, 5.0 Hz), 2.39 (1H, m), 2.13 (1H, d, *J* = 13.0 Hz), 1.82 (1H, d, *J* = 13.0 Hz), 1.32 – 1.22 (1H, m), 1.10 (1H, q, *J* = 13.0 Hz). δ_C 170.7, 137.7, 137.4, 133.3, 129.1, 128.7, 128.5, 128.1, 127.8, 127.4, 126.2, 77.4, 71.7, 62.8, 39.2, 38.9, 37.8, 37.4, 30.7. HRMS (ESI) *m/z* calcd for $C_{23}H_{26}NO_2$ $[M + H]^+$ 348.1974, found 348.1977. Key NOE correlations between H1 (3.91-3.86 ppm) and H8 (1.10 ppm); H8 (2.13 ppm) and H8a (3.54 ppm); and H7 (2.39 ppm) and CH_2Ph (4.52 ppm).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publication website at

^{1}H and ^{13}C NMR assignments, copies of the ^{1}H and ^{13}C NMR spectra of new compounds, computational details, and gaussian archive entries.

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Notes

The authors declare no competing financial interest

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