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Scope and limitations of the synthesis of functionalized quinolizidinones and related compounds by a simple precursor approach via addition of lithium allylmagnesates to 2-pyridones and RCM as key steps

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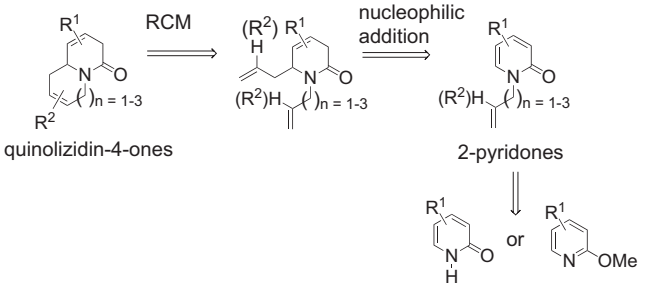
ABSTRACT

The scope and limitations of the simple synthesis of functionalized quinolizidin-4-ones by chemoselective N-alkenylation of *N*H pyridin-2(1*H*)-ones (2-pyridones), regioselective addition of lithium allyl(di-*n*-butyl)magnesates(1-) to *N*-alkenylpyridin-2(1*H*)-ones, followed by ring closing metathesis (RCM) is described. A number of functionalizations introduced into quinolizidin-4-one rings demonstrated the high prospect of the strategy proposed in scaffold synthesis. Their extension to the syntheses of pyrido[1,2-*a*]azepin-4-one and pyrido[1,2-*a*]azocin-4-one derivatives as well as to spiro-fused compounds is also presented.

1. Introduction

Quinolizidines make an important class of compounds first of all because of their widespread occurrence in nature[1,2] and because they have been identified as valuable pharmacophores.[3] A wide range of biological activities associated with the quinolizidine moiety still inspire synthetic organic chemists to develop more and more advanced methods for the synthesis of these naturally occurring compounds[4] as well as to the design and assembly of functionalized quinolizidines as drug candidates.[5] However, in accordance with current recommendations for scaffold synthesis based on natural products, the efforts in the synthetic strategy development should be focused on their simplicity, accessibility of starting materials, high degree of stereoselectivity, efficiency of transformations in minimal number of steps and possible vast diversity in the ring systems.[6]

Amongst the variety of synthetic approaches to the synthesis of quinolizidine skeleton,[7] ring closing metathesis (RCM) has become the most powerful annelation tool.[3c,4d,e,l,m,q,ac,ae,5e,8] One of the synthetic strategies towards quinolizidin-4-ones, based on RCM methodology, consists of the introduction of an allyl group into C6 of δ-lactam ring, as one of two adjacent allyl groups, by the addition reaction of allyl nucleophiles to *N*-acyliminium ions followed by annelation using ruthenium catalysts.[4d,8a,f,r] Despite undoubtedly very high importance of the above methodologies their application in scaffold synthesis is limited due to the lack of the attachment of the optional substituents in the piperidinone ring of quinolizidin-4-one. In order to avoid these restrictions we postulate to use 2-pyridones (pyridin-2(1*H*)-ones) as a functionable source of the piperidin-2-one ring (Scheme 1).



Scheme 1. Retrosynthetic approach to quinolizidin-4-one scaffold.

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Exploring the concept of the synthesis of functionalized piperidin(e)-2(1*H*)-(thi)ones,[9] we have hitherto published two preliminary reports on a simple approach to substituted 3,6,9,9a-tetrahydroquinolizin-4-ones, one achieved from pyridin-2(1*H*)-ones[10a] and the second from 2-methoxypyridines as precursor of the former[10b] (Recently, for the synthesis of substrates we also presented some results on the noncryogenic 5-functionalization of 2-methoxypyridine,[11] which can be applied as a source of pyridin-2(1*H*)-ones.). According to the strategy proposed, the regioselective addition of lithium allyl(di-*n*-butyl)magnesate(1-)[9e,f] to ring-functionalized *N*-allyl substituted pyridin-2(1*H*)-ones[9i] and ring closing metathesis (RCM) were the key steps.[10] To the best of our knowledge the above-mentioned, preliminary reported method is hitherto the only described access to both unsubstituted and substituted 3,6,9,9a-tetrahydroquinolizin-4-ones, except a multistep approach to enantiopure, unsubstituted 3,6,9,9a-tetrahydroquinolizin-4-one developed by Richards and Nomura in 2009.[8l] As a continuation of our ongoing program aimed at scaffold assemblies based on quinolizidin-4-one, achieved from readily available starting materials,[10] we now report a detailed study on the scope and limitations of the application of substituted derivatives of pyridin-2(1*H*)-ones in nucleophilic addition of lithium allyl(di-*n*-butyl) magnesate(1−) followed by RCM (Scheme 1). Within this study we also present the attempts to apply lithium allyl(di-*n*-butyl)magnesates derived from 2-methylallylmagnesium chloride and 3,3-dimethylallylmagnesium bromide and the results of further examination of usefulness of the investigated strategy for the synthesis of bicyclic piperidin-2(1*H*)-ones with seven- and eight-membered rings, which belong to pyrido[1,2-*a*]azepin-4-one and pyrido[1,2-*a*] azocin-4-one systems, respectively. Finally, we will show the synthesis of new spiro-fused quinolizidin-4-ones and related pyridoazepin-4-one consisted in one-pot installation of three allyl arms and one-pot double RCM. As an essential element of the worked out strategy, we also include in this paper, the so far not described, chemoselective procedure of N-alkylation of *N*H-substituted pyridyn-2(1*H*)-ones, which comprises N-allylation and N-alkenylation.

As to reaction types applied, it should be emphasised that although the RCM method is well established,[8,12] the nucleophilic addition to C6 of pyridin-2(1*H*)-ones still deserves more attention because it was less studied, however, the reaction often leads to valuable piperidin-2-one-like compounds.[4j,13] Amid the nucleophiles used in the addition to pyridin-2(1*H*)-ones, developed and applied by us, lithium allyl(di-*n*-butyl)magnesate(1−)[9e,f,i,10] belongs to the relatively new and useful family of 'ate' complexes, which have been recently reviewed.[14] Besides, perusal of the literature reveals that from a synthetic point of view, the alkylation of *N*H pyridin-2(1*H*)-ones is of fundamental importance as *N*-alkylated pyridin-2(1*H*)-ones are frequently used in the synthesis of potential drugs[15] and still remains a synthetic challenge in terms of N- and O-chemoselectivity.[4j,16] Furthermore, the synthesis of spiro-fused compounds was dictated by the fact of their application in medical chemistry.[17]

2. Results and discussion

At the first stage of our study, we investigated the synthesis of functionalized *N*-alkenyl substituted pyridin-2(1*H*)-ones. According to the first method (A) used, *N*H pyridin-2(1*H*)-ones (**2**) were subjected to N-alkylation. The second method (B) applied consisted in direct transformation of 5-functionalized 2-methoxypyridines (**1**) into *N*-allyl derivatives **3** by adaptation of the method developed by Bowman and Bridge.[18]

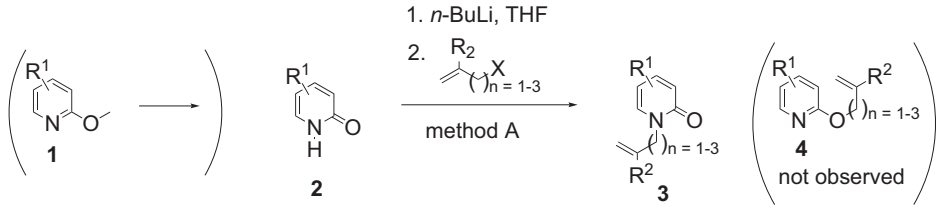
While searching for an efficient and chemoselective method for N-allylation of *N*H pyridin-2(1*H*)-ones (**2**) by varying solvents and base, we found that the simply use of *n*-BuLi in THF and subsequent use of allylbromide led to sole *N*-allylated products **3** (Table 1). It should be noted that the use of equimolar ratio of *n*-BuLi with respect to *N*H pyridin-2(1*H*)-ones (**2**) in THF solution converted **2** into colourless *N*-lithiated salt and the completion of *N*H−*N*Li exchange can be easily identified due to the appearance of yellow or beige colour upon addition of an excess of *n*-BuLi. This titration-like effect was more or less intensively observed in all *N*H-pyridones used. Furthermore, as the reaction with allylbromide occurs slowly at room temperature, leading to complete conversion in a few days, we decided to heat the reagents gently at 70 °C, which allowed a complete conversion within ca. 18–20 h. All *N*-lithiated pyridin-2(1*H*)-ones used gave chemoselectively *N*-allylated products **3** in good yields from both allylbromides and allyl chlorides, for the latter in the presence of NaI (10–20 mol %). Complete chemoselectivity and reaction progress were concluded from the ^{1}H NMR spectra of crude reaction mixtures. The results and conditions presented in Table 1 show that it is possible to prepare different ring substituted *N*-allyl, *N*-2-methyl(or chloro or phenyl)allyl pyridin-2(1*H*)-ones in a few grams scale and for liquid products simple distillation can be applied for their purification. Most of *N*H pyridin-2(1*H*)-ones used were commercially available and the other were prepared from 2-methoxypyridines by simple transformations (for details see Supplementary data).

Following these studies we also found that the above procedure can be successfully applied for the chemoselective synthesis of *N*-but-2-enyl and *N*-pent-2-enyl derivatives (Table 1, entries 21–23 and 24, respectively), however, in their syntheses more reactive electrophiles, i.e., esters of sulfonic acids, instead of bromides or iodides, should be used. In a group of sulfonates applied, only triflates (Table 1, entries 21–24) allowed to obtain *N*-alkenylated products within 3 h at room temperature, while the use of mesylate (Table 1, entries 21 and 22) and besylate (Table 1, entry 21) required 7–8 or 2 days of heating to achieve reasonable conversion, respectively.

As mentioned above, a few 5-substituted *N*-allylated pyridin-2(1*H*)-ones **3** were obtained in good yields directly from 5-functionalized 2-methoxypyridines by heating them at 55 °C for 2 days in acetonitrile with 10-fold excess of allylbromide in the presence of 2.2 equiv of NaI (Scheme 2).

At the next stage, functionalized *N*-alkenylpyridin-2(1*H*)-ones **3** were submitted to the reaction with lithium allyl(di-*n*-butyl)-magnesates(1−) **6a** and **6b** (Table 2) at a low temperature (generally at −75±5 °C). The results are summarized in Table 2. Lithium allylmagnesate complexes **6a**, **6b** were prepared immediately before use, simply by mixing of allylMgCl (**5a**) or methallylMgCl (**5b**) with 2 equiv of *n*-BuLi at 0 °C. Subsequently, the whole mixture that contained lithium allyl(di-*n*-butyl)magnesate and LiCl, was cooled down and transferred to the solution of pyridin-2(1*H*)-one **3** in THF, earlier cooled and held at −75±5 °C (It should be noted that only small excess of magnesate in relation to **3** was used (ca. 1.15 equiv)). Stirring for 25 min led to obtain 6-allylated products **7** in good yields in most reactions (Table 2). However, in the case of 5-CF_3 (**3f**), 3-OBn (**3k**), 5-NO_2 (**3g**, **3r**), and 5-(4,4,5,5-tetramethyl-[1,3,2] dioxaborolan-2-yl)- (**3aa**) substituted pyridin-2(1*H*)-ones unidentified complex mixture formation or decomposition of the substrate was observed. As far as regioselectivity of the addition of **6** to **3** is concerned all reactions proceed in regioselective manner yielding mainly 6-allylated isomer **7**. Only slight but essential influence of the substituent present at C5 of pyridin-2(1*H*)-one **3** on the regioselective 1,6–addition was observed. The lowest 1,6-regioselectivity was found for C5–Cl substituted substrates, better for compounds **3** equipped with C5–H(D) or C5–$SiMe_3$ or C5–Me substituents. However, the best 1,6-regioselectivity was observed for the addition of **6a** to pyridin-2(1*H*)-ones, which posses C5-aryl (**3h**, **3i**, **3s**, **3v**) or C5-phenylsulfanyl- (**3j**, **3t**, **3w**) or C5-phenylethynyl (**3ab**) substituents. An attempt to allylate 3-methylpyridin-2(1*H*)-one (**3d**) allowed verification of the

Table 1
Synthesis of *N*-alkenylpyridin-2(1*H*)-ones **3** by chemoselective N-alkylation of **2**

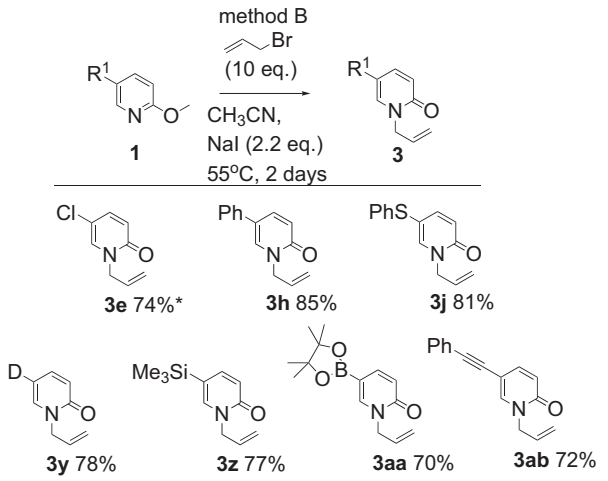


Entry	R^1	R^2	*n*	X	**3**	*T* [°C];	*t* [h];	RX [equiv]	Conversion of **2**[a] [%]	**3** Yield[b] [%]
1	H	H	1	Br	**a**	70	18	1.3	>99	95[c] (99)[2]
						22	144	3.0	98	81[c] (81)[2]
2	5-Me	H	1	Br	**b**	70	18	1.3	>99	82[c] (85)[2]
3	4-Me	H	1	Br	**c**	70	18	1.3	>99	84[c] (84)[2]
4	3-Me	H	1	Br	**d**	70	19	1.3	>99	86[c] (90)[2]
						22	96	2.5	>99	82[c]
5	5-Cl	H	1	Br	**e**	70	18	2.0	>99	86[c] (94)[2]
						22	72	3.0	>99	84[c] (94)[1]
6	5-CF_3	H	1	Br	**f**	70	18	1.3	>99	85[c] (93)[1]
7	5-NO_2	H	1	Br	**g**	22	24	3.0	99	72[d]
8	5-Ph	H	1	Br	**h**	70	20	1.3	>99	91[d]
9	5-(4-FC_6H_4)	H	1	Br	**i**	70	20	1.2	>99	86[d]
10	5-SPh	H	1	Br	**j**	70	17	1.2	>99	92[d]
11	3-OBn	H	1	Br	**k**	70	20	1.3	>99	86[d]
12	H	Me	1	Br	**l**	70	20	1.3	>99	78[c] (86)[1]
				Cl[e]		70	20	2.0	>99	91[c] (97)[2]
13	5-Cl	Me	1	Cl[f]	**m**	70	20	1.3	>99	82[c] (89)[2]
14	H	Cl	1	Cl[f]	**n**	70	20	1.3	86	70[c] (76)[2]
15	4-Me	Cl	1	Cl[f]	**o**	70	20	1.3	98	73[c] (82)[2]
16	H	Ph	1	Br	**p**	70	20	1.2	>99	90[d] (91)[2]
17	5-Cl	Ph	1	Br	**q**	70	20	1.2	>99	95[d] (99)[2]
18	5-NO_2	Ph	1	Br	**r**	70	20	1.2	>99	81[d] (83)[2]
19	5-Ph	Ph	1	Br	**s**	70	20	1.2	>99	85[d] (87)[2]
20	5-SPh	Ph	1	Br	**t**	70	20	1.2	~92	78[d] (78)[2]
21	H	H	2	Br[g]	**u**	65	9	1.3	~88	33[h]
				OMs		70	168	1.2	~94	79[c]
				SO_3Ph		70	48	1.2	>99	71[c] (84)[2]
				OTf		22	2.5	1.2	>99	91[d] (94)[2]
22	5-Ph	H	2	OMs	**v**	70	192	1.2	94	82[d]
				OTf		22	2.5	1.2	>99	87[d]
23	5-SPh	H	2	OTf	**w**	22	3.0	1.2	>99	95[d]
24	H	H	3	Br[g]	**x**	68	5.5	1.3	~90	36[d,h]
				Br[i]		70	96	1.3	~72	53[c] (56)[2]
				OTf		22	1.5	1.2	>99	93[j] (97)[1]

[a] Conversion estimated using ^{1}H NMR spectroscopy of crude reaction mixture.
[b] Isolated yields. Yields estimated by ^{1}H NMR spectroscopy using internal reference are given in the parenthesis. The number of determinations is given in the upper index.
[c] Product was isolated in pure state by distillation.
[d] Product was isolated in pure state by column chromatography.
[e] NaI (20 mol %) was added.
[f] NaI (10 mol %) was added.
[g] K_2CO_3 (1.3 equiv) and anhydrous acetone were used instead of *n*-BuLi and THF.
[h] In this reaction additionally 9% of *O*-alkylated isomer was formed.
[i] NaI (30 mol %) was added.
[j] Product was isolated in pure state by distillation and the residue was purified by column chromatography.

stereoselectivity at C-3. In this reaction, low stereoselectivity was observed yielding trans and cis isomers of **7f**, quoted further as **7f**-*trans* and **7f**-*cis*, in the ratio of 6:4, respectively. Fortunately, these compounds were obtained in diastereoisomerically pure state by separation using flash column chromatography. For the sake of comparison **3a**, **3b** and **3j** were exposed to allylMgCl (**5a**) under the same temperature as for allyl(*n*-Bu_2)MgLi (**6a**). The results confirmed a lower reactivity of allylMgCl in relation to that of allyl(*n*-Bu_2)MgLi[9e,f] and also showed that reactions conducted with the use of magnesates **6** led to the pure products, while the application of sole Grignard reagent produced impurities, probably of C–C coupling origin, which were difficult to remove (e.g., Table 2, entry 12). In the light of the recent investigation on the structure and reactivity of allylmagnesates,[19] the explanation of the improved reactivity of **6** in relation to **5** can be considered in terms of coordination modes of allyl moieties. However, to support this hypothesis, more detailed studies on complexes of **6** are required.

Finally, functionalized *N*-alkenyl,6-allyl β,γ-unsaturated δ-lactams **7** were annelated by RCM (Table 3), employing, in general, Grubbs first (**GI**) and/or more efficient Grubbs second (**GII**) generation catalyst, with the exception of 6-allyl-*N*-(2-phenylallyl) derivatives **7q**, **7r**, **7t** and **7u**, for which Stewart–Grubbs catalyst (**S**–**G**) was used. (The attempt to apply **GII** for **7q** brought much worse outcome [see Table 3, entry 18]). The optimal conditions found for **S**–**G** cat., required 1.6–1.9 mol % loading of catalyst, temperature 75 °C and reaction time up to 140 min (TLC-control) (Table 3, entries 18–21). It should be noted that Stewart–Grubbs catalyst (**S**–**G**) was hitherto used to increase the efficiency in cross-metathesis (CM)[20] and RCM reactions of sterically hindered olefins (except phenylvinyl derivatives)[21] or in ring-rearrangement



Scheme 2. Direct synthesis of *N*-allylpyridin-2(1*H*)-ones from 2-methoxypyridines (*5 days of heating was applied).

metathesis (RRM).[22] Only recently, Stewart–Grubbs catalyst was used in the RCM synthesis, in which 2-phenyacryloyl arm participated.[23] Furthermore, the extension of the above methodology for the synthesis of derivatives with newly formed seven- (**9v**–**9x**, Table 3, entries 22–24) and eight-membered (**9y**, Table 3, entry 25) rings was successful. Bicyclic compounds **9v**–**9x** were obtained in good yields, however, in the case of formation of eight-membered ring (**9y**, Table 3) 10% of *E* isomer was also formed.

Regrettably, two diallylated δ-lactams **7p**, **7ad** give no positive results in RCM. One lactam possesses *N*-(2-chloroallyl) moiety (**7p**) and other one has 5-phenylethynyl substituent (**7ad**). Although, on the basis of the literature reports, the connection of allyl and chlorovinyl arms can be expected to occur,[24] three attempts to obtain product **9q** from **7p** failed (Table 3, entry 17), albeit, traces of the product formation were observed when larger amount of catalyst **GII** was used. When using 5-phenylethynyl-1,6-diallyl derivative **7ad**, RCM product was not observed and the substrate was recovered in 70% (Table 3, entry 14). Although difficulties in annelation of vinylchlorides by RCM have been well established,[25] no annelation process observed for 5-phenylethynyl 1,6-diallyl derivative **7ad** was surprising. This lack of reactivity may result from Fischer-type carbene complex formation, which, being 'locked' by coordination of alkyne π-electrons, failed to react further. Similar, unsuccessful RCM annelation of adjacent alkenyl groups in the presence of alkynyl moiety was observed in β-carboline synthesis.[26]

As previously mentioned we wanted to expand the allylation step for using lithium di-*n*-butyl(3,3-dimethylallyl)magnesate **6c** but the attempt partly failed, because in the reaction with **3a** mainly 4-allylated isomer **10a** was formed in 63% yield together with only small amounts (15% yield) of 1:1 mixture of 6-allylated isomers **11a** and **11b** (Scheme 3, upper part). Albeit, forcing the reaction towards 6-allylation by submission of **6c** to the reaction with 4-methylpyridin-2(1*H*)-one (**3c**), resulted in the addition at C6 in moderate yields, but still as 1:1 inseparable mixture of isomers (**12a**, **12b**) (Scheme 3, lower part). Fortunately, treatment of this mixture with catalyst **GI** succeeded in accomplishing 9-dimethyl-substituted quinolizidin-4-one **13** from the corresponding 1,1-dimethylallyl isomer **12b**, while isomer **12a** remained unchanged.

At the end of our study, we also briefly explore the possibilities of the synthesis of quinolizidin-4-ones and its bicyclic analogs equipped with spiro-fused five-membered rings in two steps starting from **3** (Scheme 4). Because addition of lithium allyl(di-*n*-butyl)magnesates to *N*-alkylated pyridin-2(1*H*)-ones followed by the reaction with excess of allylbromide allowed the introduction of two adjacent 3-allyl groups in one step,[9i] we decided to apply this reaction as the first step of the planned synthesis of spiro-fused derivatives. However, because the reactions described were not fully regioselective, yielding 3,3-diallylation and 3,5-diallylation products in ca. 8:2 ratio,[9i] we used 5-phenyl and 5-phenysulfanyl derivatives (**3h**, **3v**, **3w**) with occupied C5 position. Besides, the selected compounds led to the highest regioselectivity in the reaction with allyl(di-*n*-butyl)magnesate **6a**. The second step comprised one-pot double RCM. As a result, the syntheses of spiroquinolizidin-4-ones **15a**–**15c** were accomplished only in two steps starting from **3** leading to both tetraalkenylated intermediates **14** and spiro-compounds **15** in good yields as depicted in Scheme 4.

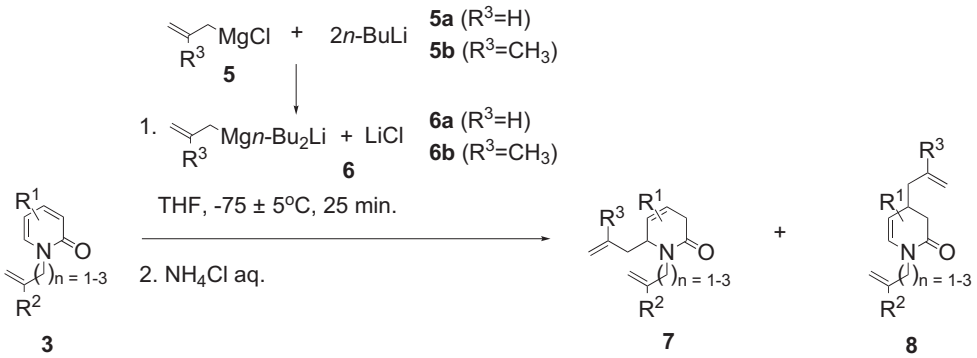
In the overall assessment, the protocol described seemed to be useful for quinolizidin-4-ones scaffold synthesis as well as for related bicyclic piperidinones and spiro-fused compounds, in spite of medium tolerance of functional groups during the addition and the annelation step. In the light of search for potential drugs, from among the achievements obtained, the most valuable seemed to be the synthesis of derivatives **9** and **15** equipped with aryl groups as their presence often enhances biological activities.[27]

The structures of compounds **3**, **7**, **9**, **10a**, **12a**, **13**–**15** were elucidated with the aid of 1D NMR (^{1}H,^{13}C, ^{13}C-DEPT-135) and 2D NMR spectroscopy (^{1}H,^{1}H COSY; ^{1}H,^{13}C HETCOR), IR spectroscopy, mass spectra and HRMS analyses. The configurations of products **7f**-*trans*, **7**-*cis* and **9f**, **9g** were determined on the basis of 1D NOE experiments and 2D ^{1}H,^{1}H NOESY spectra, respectively. Compounds **7** and **8** were easily analyzed by TLC and because of their different polarity were separated by column chromatography without problems. However, due to low yields of regioisomers **8**, only six of them (**8a**, **8b**, **8c**, **8g**, **8z**, **8ab**) were isolated in purity permitting their structural analyses by NMR, IR and GC–MS methods. As far as distinction of regioisomers **7** and **8** is concerned, the inspection of ^{1}H and ^{13}C NMR spectra (including routine ^{13}C DEPT-135 experiments) of both regioisomers **7** and **8** (see Supplementary data), showed that in general, ^{13}C NMR chemical shifts of CH-6 groups found in the spectra of regioisomers **7** in ~61–56 ppm region, in comparison to ^{13}C NMR chemical shifts of CH-4 groups observed in spectra of regioisomers **8**, appearing in the range ~39–30 ppm, are the best criteria for simple distinction of both regioisomers. This observation is supported by ^{13}C NMR and ^{13}C DEPT-135 NMR spectra of 4-(1,1-dimethylallyl) substituted, major regioisomer **10a**, in which the resonance signal assigned to CH-4 appears at 41.5 ppm. Furthermore, although the ^{1}H NMR spectra of both regioisomers **7** and **8** are less useful for their distinction because the resonance positions and multiplicities of ^{1}H NMR signals are strongly affected by substituents, the most characteristic differences appear in the resonance positions of signals originating from NCH_2 of *N*-allyl groups. For 6-allylated isomers **7** diastereotopic NCHH protons give resonance signals distant from each other by ~1.1–1.8 ppm, while for compounds **8** the difference between chemical shifts of NCHH is much smaller, of about ~0.1 ppm with average chemical shits of NCHH at ~4.1 ppm for both isomers.

3. Conclusions

In conclusion, we have demonstrated that the 1,6 regioselective addition of lithium allyl(or 2–methylallyl)(di-*n*-butyl) magnesate(1–) reagent to substituted in the ring *N*-alkenylpyridin-2(1*H*)-ones, followed by RCM, provided easy access to racemic, functionalized 3,6,9,9a-tetrahydroquinolizin-4-ones, having substituents and C–C double bonds in both rings. The protocol described, enables their extension for the synthesis of substituted bicyclic piperidin-2-ones (pyridoazepin-4-ones and pyridoazocin-4-one) and of spiro-functionalized quinolizidin-4-ones and pyridoazepin-4-ones. Both, typical and extended procedures

Table 2
Synthesis of 6-allyllactams **7** by regioselective addition of lithium (meth)allyl(di-*n*-butyl)magnesates **6** to *N*-alkenylpyridin-2(1*H*)-ones **3**



Entry	R^1	R^2	R^3	*n*	**5**, **6**	**7**, **8**	*T* [°C]	**7**/**8**[a]	Conversion of **3**[a]	**7** Yield[b] [%]
1	H	H	H	1	**5a**[c]	**a**	−70	76:24	54	27
					5a[d]		−80	88:12	92	49
					6a		−70	99:1	>99	81
2	H	H	Me	1	**6b**	**b**	−72	94:6	92	74
3	5-Me	H	H	1	**5a**[c]	**c**	−80	68:32	85	44
					6a		−80	92:8	>99	93
4	4-Me	H	H	1	**6a**	**d**	−65	100:0	>99	90
5	4-Me	H	Me	1	**6b**	**e**	−72	100:0	93	81
6	3-Me	H	H	1	**6a**	**f**	−70	92:[e]8	>99	82
7	5-Cl	H	H	1	**6a**	**g**	−72	87:13	89	58
8	5-CF_3	H	H	1	**6a**	**h**	−78	—:—[f]	99	0[f]
9	5-NO_2	H	H	1	**6a**	**i**	−78	—:—[f]	99	0[f]
10	5-Ph	H	H	1	**6a**	**j**	−74	>99:1	>99	88
11	5-(4-FC_6H_5)	H	H	1	**6a**	**k**	−74	>99:1	>99	90
12	5-SPh	H	H	1	**5a**[d]	**l**	−78	99:1	~95	58[g]
					6a		−78	>99:1	>99	75
13	3-OBn	H	H	1	**6a**	**m**	−80	—:—[f]	>99	0[f]
14	H	Me	H	1	**6a**	**n**	−80	94:6	>99	74
15	5-Cl	Me	H	1	**6a**	**o**	−80	87:13	>99	67
16	H	Cl	H	1	**6a**	**p**	−80	96:4	97	73
17	H	Ph	H	1	**6a**	**q**	−80	95:5	>99	87
18	5-Cl	Ph	H	1	**6a**	**r**	−80	88:12	>99	79
19	5-NO_2	Ph	H	1	**6a**	**s**	−80	—:—[f]	>99	0[f]
20	5-Ph	Ph	H	1	**6a**	**t**	−80	>99:1	>99	82
21	5-SPh	Ph	H	1	**6a**	**u**	−78	>99:1	>99	90
22	H	H	H	2	**6a**	**v**	−72	>99:1	>99	82
23	5-Ph	H	H	2	**6a**	**x**	−78	>99:1	>99	83
24	5-SPh	H	H	2	**6a**	**y**	−80	>99:1	>99	81
25	H	H	H	3	**6a**	**z**	−72	94:6	96	84
26	5-D	H	H	1	**6a**	**aa**	−72	95:5	>99	79
27	5-TMS	H	H	1	**6a**	**ab**	−78	95:5	>99	76
28	5-()	H	H	1	**6a**	**ac**	−80	—:—	>99	0[h]
29	5-Ph-C≡C	H	H	1	**6a**	**ad**	−74	>99:1	>99	84

[a] Estimated using ^{1}H NMR spectroscopy of crude reaction mixture.
[b] Isolated yields.
[c] 1.5 equiv was used.
[d] 2.0 equiv was used and stirred 1 h.
[e] Product **7f** was isolated as trans (**7f** (trans))/cis (**7f** (cis)) mixture of isomers in 6:4 ratio.
[f] The complex mixture was obtained.
[g] Product can not be obtained in pure state.
[h] Decomposition of substrate.

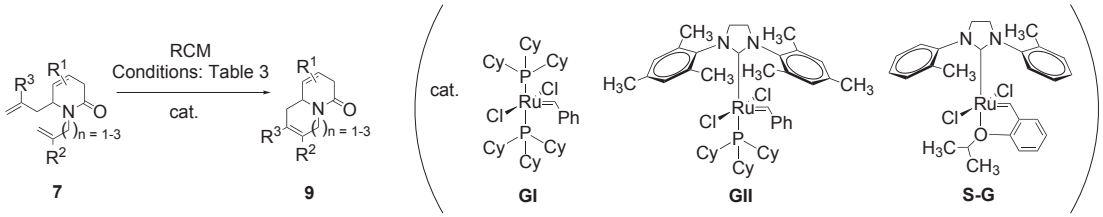
comprised the synthesis of the intermediate β,γ-unsaturated δ-lactams, in which the substituent originated from the starting *N*-alkenylpyridin-2(1*H*)-ones, which in turn were obtained by chemoselective N-alkenylation. Due to great basic potential of magnesate complexes, novel spiro-fused compounds were obtained from *N*-alkenylpyridin-2(1*H*)-ones only in two steps. The relatively high degree of functionalization and potentially possible further derivatization of RCM products[28] indicate high prospect of 3,6,9,9a-tetrahydroquinolizin-4-ones and related bicyclic compounds in scaffold synthesis. Design and synthesis of functionalized quinolizidines on the basis of the above procedure, aimed at obtaining derivatives showing anticancer activity are currently under way.

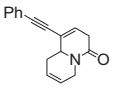
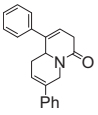
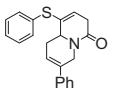
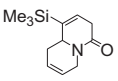
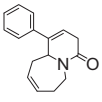
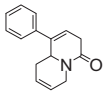
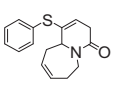
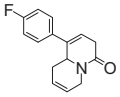
4. Experimental section

4.1. General

Melting points were determined on a Boetius hot stage apparatus. ^{1}H, ^{13}C NMR spectroscopic measurements were performed on a Bruker DPX 400 spectrometer equipped with a 5 mm 1H/BB-inverse probehead, operating at 400.1 and 100.6 MHz. TMS was used as internal reference. For resolving of multiplets in ^{1}H NMR spectra ACD/SpecManager program (version 12.01) was used. For detailed peak assignments, 2D spectra were acquired using standard Bruker software (COSY, HETCOR). In the ^{1}H–^{1}H NOESY

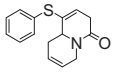
Table 3
RCM of **7**



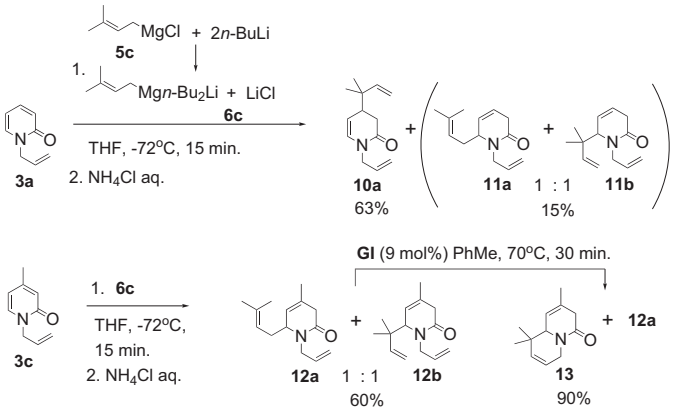
Entry	9	9	Cat.[a] (mol %)	Temp (°C)	Time (min.)	Yield[b] (%)	Entry	9	9	Cat.[a] (mol %)	Temp (°C)	Time (min.)	Yield[b] (%)
1	**a**		**GI** (6) **GII** (1.0)	22 70	60 20	83 89	14	**n**		**GII** (2.0)	70	120	0[d]
2	**b**		**GII** (0.7)	70	15	87	15	**o**		**GII** (1.1)	70	20	79
3	**c**		**GI** (8) **GII** (0.9)	22 70	60 20	75 83	16	**p**		**GII** (1.4)	70	20	93
4	**d**		**GI** (6) **GII** (1.1)	22 70	60 20	75 85	17	**q**		**GII** (3.5) **GII** (7) **S–G** (3.5)	75 70 75	60 120 1200	0[e] Traces[f] 0[e]
5	**e**		**GII** (0.7)	70	20	80	18	**r**		**GII** (10) **S–G** (1.7)	70 75	120 120	16 80
6	**f**		**GI** (7) **GII** (1.0)	22 70	45 20	82 83	19	**s**		**S–G** (1.6)	75	140	91
7	**g**		**GI** (4) **GII** (1.2)	22 70	60 20	75 80	20	**t**		**S–G** (1.9)	75	80	66
8	**h**		**GII** (1.4)	70	30	82	21	**u**		**S–G** (1.7)	75	100	76
9	**i**		**GI** (7)[c]	70	20	73	22	**v**		**GI** (7) **GII** (1.5)	22 70	45 30	73 82
10	**j**		**GII** (2.5)	70	20	95	23	**w**		**GII** (1.0)	70	30	83
11	**k**		**GII** (2.5)	70	15	78	24	**x**		**GII** (1.1)	70	30	91
12	**l**		**GII** (1.9)	70	20	87	25	**y**		**GII** (1.0)	70	45	75[g]

(*continued on next page*)

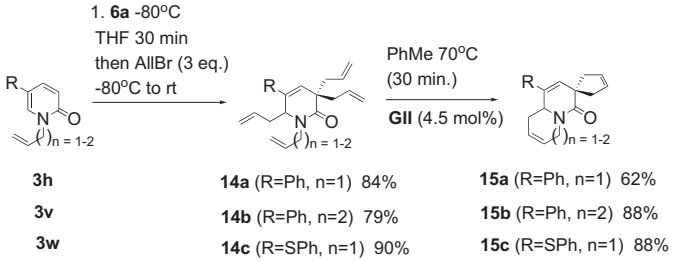
Table 3 (*continued*)

Entry	9	9	Cat.[a] (mol %)	Temp (°C)	Time (min.)	Yield[b] (%)	Entry	9	9	Cat.[a] (mol %)	Temp (°C)	Time (min.)	Yield[b] (%)
13	**m**		**GII** (4.0) **GII** (2.0)	70 70	20 20	83 79							

[a] For **GI**, CH_2Cl_2 at 22 °C, for **GII**, toluene at 70 °C and for **S**–**G**, toluene at 75 °C were used unless stated otherwise.
[b] Isolated yields.
[c] Toluene was used as solvent.
[d] Not detected by GC–MS nor ^{1}H NMR. Substrate was recovered in 70%.
[e] Substrate was unchanged. Not detected by GC–MS.
[f] Detected by GC–MS.
[g] Product contained 10 mol % of isomer trans.



Scheme 3. An attempt to apply magnesate **6c** in the synthesis of quinolizidin-4-ones.



Scheme 4. Two-step synthesis of spiro-fused compounds **15**.

experiments a mixing time of 0.75 s was used. The abbreviation 'dm' in description of ^{1}H NMR spectra means doublet of multiplet. It describes more complex couplings including one large coupling constant. Gas chromatography–mass spectrometry (GC–MS) measurements were carried out on a Hewlett–Packard instrument model HP 6890 equipped with a mass detector HP 5973. Infrared spectra were taken with a Specord M80 or ALPHA FT-IR instruments. HRMS analyses (ESI^+) were performed on a Waters LCT premier XE (TOF) using acetonitrile as solvent. Low temperature was generated by Julabo FT902 immersion cooler. Reactions in tetrahydrofuran (THF) solution were performed under argon in flame-dried flasks and liquid components were added by syringe. THF, toluene were purified over sodium, CH_2Cl_2 over calcium hydride, both in argon atmosphere according to a standard procedure prior to use. Products were purified by flash column chromatography on silica gel (0.04–0.063 mm, Merck).

4.2. Compounds and reagents

Amongst *N*H pyridin-2(1*H*)-one used 3-benzyloxypyridin-2(1*H*)-one was obtained from 3-hydroxypyridin-2(1*H*)-one,[29] while pyridin-2(1*H*)-one their 3-methyl-, 4-methyl-, 5-methyl-, 5-chloro-, 5-trifluoro- and 5-nitrosubstituted derivatives were supplied from commercial sources. AllMgCl (2.0 M in THF), metallMgCl (0.5 M in THF), *n*-BuLi (2.5 M in hexane) and ruthenium catalysts as well as 3-bromopropene, 4-bromobut-1-ene, 5-bromopent-1-ene, 3-bromo-2-methyl-propene, 2,3-dichloropropene were purchased from Aldrich. (1-Bromo-methylvinyl)benzene[30] and but-3-en-1-yl-, pent-4-en-1-sulfonates,[31] 3,3-dimethylallylmagnesium bromide[9f] and 5-deuterium-, 5-chloro-, 5-phenylsulfanyl-, 5-trimethylsilanyl- and 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-substituted 2-methoxypyridines[11] were prepared according to procedure described earlier.

4.3. General procedure for N-chemoselective alkenylation of 2

To a cooled (~0 °C) and stirred solution of *N*H pyridin-2(1*H*)-one **2** (7.8 mmol) in anhydrous THF (50 mL) in a 100 mL Schlenk flask equipped with septum and argon balloon, *n*-BuLi (7.8 mmol, 3.2 mL, 2.5 M in hexane) was added via syringe over a few minutes and the mixture was stirred for 5 min.[†] To a cooled (−2 to 0 °C) solution alkyl halides or sulfonates [9.4–15.6 mmol (see Table 1)] were added via syringe. The resulting solution was stirred for 10 min. Subsequently, in most reactions (see Table 1) the septum was removed and the flask was equipped with condenser crowned with argon balloon and placed in oil bath at 70±1 °C. The mixture was continuously stirred for appropriate time (Table 1). After cooling to rt and addition of aqueous saturated NH_4Cl (15 mL), the aqueous layer was extracted with ethyl acetate (3×80 mL) and combined organic layers[‡] were dried over $MgSO_4$. Filtration, concentration in vacuo and purification by distillation or flash column chromatography (see Table 1) yielded **3**.

4.4. General procedure for addition of lithium allyl(di-*n*-butyl)magnesates to pyridin-2(1*H*)-ones. Synthesis of 7, 8, 10, 12 and 14

On stirring, to a cooled (0 °C) solution of allylMgCl (4.9 mmol, 2.45 mL, 2.0 M in THF) in dry THF (10 mL) in a Schlenk flask, *n*-BuLi (9.8 mmol, 3.9 mL, 2.5 M in hexane) was added via syringe over 3 min under argon. A pale yellow solution was stirred for 5 min and cooled to −75±5 °C. The suspension containing lithium allyl(di-*n*-

[†] *n*-BuLi was added until the solutions become permanently pale yellow or beige.
[‡] For sulfonates, the combined organic extracts were additionally washed with saturated aqueous $NaHCO_3$.

butyl)magnesate was next transferred via syringe to a cooled (−75±5 °C) solution of *N*-alkenylpyridin-2(1*H*)-one **3** (4.25 mmol) in THF (40 mL). The resulting brown-orange solution was stirred for 25 min at −75±5 °C. After quenching with aqueous saturated NH_4Cl[§] (10 mL) and warming up to rt, the aqueous layer was extracted with ethyl acetate (3×75 mL) and the combined organic layers were dried over $MgSO_4$. Filtration, concentration in vacuo and purification by flash column chromatography yielded target product.

4.5. General procedure for RCM. Synthesis of compounds 9, 13, 15

Detailed conditions for RCM synthesis are collected in Table 3. To a solution of diallyllactam **7** or tetraalkenyllactam **14** (1.0 mmol) in dry, degassed solvent (8 mL), adequate ruthenium catalyst **GI** (4–5 mol %, ~33–66 mg) or **GII** (0.7–4 mol %, ~6–34 mg) or **S**–**G** (1.6–1.9 mol %, ~9–11 mg) (see Table 3) was added and the reaction mixture was stirred under slowly bubbled stream of argon at temperature and time indicated in Table 3. Then the solvent was evaporated at reduced pressure and the residue was left standing for 48 h followed by purification on column chromatography.

*4.5.1. (±)-3,6,9,9a-Tetrahydroquinolizin-4-one (**9a**).* Colourless oil (133 mg, 89% yield). The crude product was purified by column chromatography (SiO_2, diethyl ether); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ=2.04–2.20 (m, 1H, C*H*H-9), 2.28 (1H, dquint, *J*=16.9, 2.5 Hz, C*H*H-9), 3.00 (br s, 2H, CH_2-3), 3.49 (br d, *J*=ca. 18.6 Hz, 1H, NC*H*H), 4.04–4.10 (m, 1H, CH-9a), 4.90 (dm, *J*=ca. 18.6 Hz, 1H, NCH*H*), 5.66–5.85 (m, 4H, 4×=CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=31.8, 33.5, 41.8, 54.2, 121.2, 124.1, 124.4, 125.0, 166.4; GC–MS (70 eV): 149 (100) [M^+], 148 (67), 134 (8), 120 (27), 106 (12), 96 (13), 80 (18), 67 (32), 54 (30), 39 (24); IR (film): ν=3036, 2896, 2844, 1662, 1632, 1462, 1448, 1408, 1356, 1328, 1252, 1168, 760, 722, 662 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calcd for $C_9H_{12}NO$, 150.0919; found 150.0926.

*4.5.2. (±)-8-Methyl-3,6,9,9a-tetrahydroquinolizin-4-one (**9b**).* Colourless oil (142 mg, 87% yield). The crude product was purified by column chromatography (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ=1.70–1.73 (m, 3H, 8-CH_3), 2.10 (dm, *J*=7.6 Hz, 2H, CH_2-9), 2.97–3.01 (m, 2H, CH_2-3), 3.43 (dm, *J*=18.3 Hz, 1H, NC*H*H), 4.02–4.11 (m, 1H, CH-9a), 4.85 (dm, *J*=18.3 Hz, 1H, NCH*H*), 5.38–5.43 (m, 1H, =CH-7), 5.67–5.78 (m, 2H, =CH-1, =CH-2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.9, 31.9, 38.1, 41.6, 54.1, 118.1, 121.2, 125.0, 131.7, 166.2; GC–MS (70 eV): 163 (100) [M^+], 162 (31), 148 (22), 134 (15), 120 (22), 96 (31), 80 (11), 68 (25), 67 (32), 53 (11), 41 (11), 39 (11); IR (film): ν=3072, 2952, 1642, 1446, 1408, 1356, 1328, 1248, 1108, 788, 732 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calculated for $C_{10}H_{14}NO$, 164.1075; found 164.1077.

*4.5.3. (±)-1-Methyl-3,6,9,9a-tetrahydroquinolizin-4-one (**9c**).* Colourless oil (135 mg, 83% yield). The crude product was purified by column chromatography (SiO_2, diethyl ether); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ=1.76 (d, *J*=1.7 Hz, 3H, CH_3), 2.00–2.11 (m, 1H, C*H*H-9), 2.47 (dm, *J*=ca. 16.9 Hz, 1H, C*H*H-9), 2.97 (d, *J*=1.7 Hz, 2H, CH_2-3), 3.44 (dm, *J*=18.5 Hz, 1H, NC*H*H), 3.90 (dq, *J*=11.3, 3.6 Hz, 1H, CH-9a), 4.98 (dm, *J*=18.5 Hz, 1H, NCH*H*), 5.44 (br s, 1H, =CH-2), 5.70–5.76 (m, 1H, =CH), 5.79–5.86 (m, 1H, =CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.7, 31.7, 32.1, 41.9, 57.9, 116.9, 124.4, 124.6, 131.1, 166.5; GC–MS (70 eV): 163 (100) [M^+], 162 (70), 148 (30), 134 (13), 120 (16), 110 (12), 94 (12), 81 (27), 80 (67), 54 (37), 53 (24), 39 (27); IR (film): ν=3032, 2908, 2884, 2844, 1664, 1638, 1466, 1250, 1070, 808, 662 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calculated for $C_{10}H_{14}NO$, 164.1075; found 164.1088.

*4.5.4. (±)-2-Methyl-3,6,9,9a-tetrahydroquinolizin-4-one (**9d**).* Colourless oil (138 mg, 85% yield). The crude product was purified by column chromatography (SiO_2, diethyl ether); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ=1.73 (s, 3H, CH_3), 2.01–2.13 (m, 1H, C*H*H-9), 2.25 (dm, *J*=ca. 17.1 Hz, 1H, C*H*H-9), 2.83–2.99 (m, 2H, CH_2-3), 3.49 (d, *J*=18.8 Hz, 1H, NC*H*H), 4.02 (br dm, *J*=ca. 6.4 Hz, 1H, CH-9a), 4.87 (d, *J*=18.8 Hz, 1H, NCH*H*), 5.42 (br s, 1H, =CH-1), 5.68–5.75 (m, 1H, =CH), 5.77–5.83 (m, 1H, =CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=21.8, 33.7, 36.3, 41.9, 54.1, 119.3, 124.2, 124.2, 124.2, 129.1, 166.8; GC–MS (70 eV): 163 (100) [M^+], 162 (79), 148 (67), 134 (21), 120 (22), 110 (25), 94 (18), 81 (39), 80 (89), 54 (49), 53 (34), 41 (22), 39 (36); IR (film): ν=3036, 2892, 2840, 1640, 1448, 1408, 1356, 1298, 1248, 816 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calcd for $C_{10}H_{14}NO$, 164.1075; found 164.1070.

*4.5.5. (±)-2,8-Dimethyl-3,6,9,9a-tetrahydroquinolizin-4-one (**9e**).* Colourless oil (142 mg, 80% yield). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate, 1:1 then 4:6); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ=1.70 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.01–2.10 (m, 2H, CH_2-9), 2.80–2.95 (m, 2H, CH_2-3), 3.42 (br d, *J*=18.3 Hz, 1H, NC*H*H), 3.95–4.05 (m, 1H, CH-9a), 4.82 (dm, *J*=18.3 Hz, 1H, NCH*H*), 5.38–5.43 (m, 2H, =CH-1, =CH-7); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=21.9, 22.9, 36.5, 38.4, 41.6, 54.0, 118.0, 119.4, 129.2, 131.8, 166.4; GC–MS (70 eV): 177 (100) [M^+], 176 (38), 162 (49), 148 (12), 134 (18), 110 (51), 94 (12), 80 (17), 68 (18), 67 (22), 53 (11); IR (film): ν=2964, 2912, 1642, 1448, 1408, 1298, 1112, 820 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calculated for $C_{11}H_{16}NO$, 178.1232; 178.1231.

*4.5.6. (±)-trans-3-Methyl-3,6,9,9a-tetrahydroquinolizin-4-one (**9f**).* Colourless oil (135 mg, 83% yield). The crude product was purified by column chromatography (SiO_2, diethyl ether/*n*-hexane 7:3); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ=^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.34 (d, *J*=7.5 Hz, 3H, 3-CH_3), 2.04–2.16 (m, 1H, C*H*H-9), 2.26 (dm, *J*=16.7 Hz, 1H, C*H*H-9), 2.96–3.07 (m, 1H, CH-3), 3.49 (dm, *J*=18.8 Hz, 1H, NC*H*H), 4.02–4.14 (m, 1H, CH-9a), 4.90 (dm, *J*=18.8 Hz, 1H, NCH*H*), 5.65–5.85 (m, 4H, 4×=CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.1, 33.4, 35.5, 41.9, 54.0, 123.7, 124.0, 124.6, 127.6, 170.0; GC–MS (70 eV): 163 (43) [M^+], 148 (100), 134 (7), 120 (8), 80 (28), 54 (19), 53 (18), 39 (15); IR (film): ν=3016, 2928, 2840, 1664, 1642, 1464, 1444, 1356, 1324, 1248 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calcd for $C_{10}H_{14}NO$, 164.1075; found 164.1073.

*4.5.7. (±)-cis-3-Methyl-3,6,9,9a-tetrahydroquinolizin-4-one (**9g**).* Colourless oil (130 mg, 80% yield). The crude product was purified by column chromatography (SiO_2, diethyl ether); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ=1.32 (d, *J*=7.4 Hz, 3H, 3-CH_3), 2.02–2.14 (m, 1H, C*H*H-9), 2.29 (dm, *J*=16.5 Hz, 1H, C*H*H-9), 2.98 (ddq, *J*=11.1, 7.3, 3.7 Hz, 1H, CH-3), 3.49 (dm, *J*=18.7 Hz, 1H, NC*H*H), 4.03 (dq, *J*=11.3, 3.4 Hz, 1H, CH-9a), 4.86 (dm, *J*=18.7 Hz, 1H, NCH*H*), 5.65–5.84 (m, 4H, 4×=CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=20.6, 34.1, 36.3, 42.1, 54.3, 123.7, 124.1, 124.6, 127.8, 170.3; GC–MS (70 eV): 163 (34) [M^+], 148 (100), 134 (5), 120 (8), 105 (7), 91 (7), 80 (30), 54 (23), 53 (19), 41 (15), 39 (22); IR (film): ν=3040, 2964, 2928, 2892, 2840, 1662, 1638, 1464, 1446, 1356, 1328, 1250, 766, 722, 660 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calcd for $C_{10}H_{14}NO$, 164.1075; found 164.1070.

*4.5.8. (±)-1-(^{2}H)-3,6,9,9a-Tetrahydroquinolizin-4-one (**9h**).* Colourless oil (123 mg, 82% yield). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate, 6:4 then 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ=2.06–2.17 (m, 1H, C*H*H-3), 2.28 (dm, *J*=ca. 17.1 Hz, 1H, C*H*H-3), 2.97–3.02 (m, 2H,

[§] In the synthesis of **14a**–**c**, allylbromide (1.11 mL, 12.8 mmol) instead of NH_4Cl was added and the solution was warmed to 0 °C over 30 min and stirred at 0 °C for over 30 min then at rt 1 h.

CH_2-9), 3.49 (dm, *J*=18.8 Hz, 1H, NC*H*H), 4.04–4.12 (m, 1H, CH-9a), 4.90 (dm, *J*=18.8 Hz, 1H, NCH*H*), 5.69–5.85 (m, 3H, =CH-2, =CH-7, =CH-8); ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ*=31.8, 33.5, 41.8, 54.1, 121.1, 124.1, 124.1, 124.5, 124.7 (t, J_{CD}=24.9 Hz, C-1), 166.3; GC–MS (70 eV): 150 (100) [M^+], 149 (65), 121 (22), 107 (9), 97 (11), 81 (12), 68 (26), 54 (27), 39 (11). IR (film): *ν*=3036, 2968, 2892, 2840, 1632 br, 1462, 1448, 1408, 1324, 1302, 1252, 1104, 1070, 756, 700, 664 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calcd for $C_9H_{11}DNO$, 151.0981; found 151.0997.

*4.5.9. (±)-1-Trimethylsilanyl-3,6,9,9a-tetrahydroquinolizin-4-one (**9i**).* Colourless oil (161 mg, 73% yield). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): *δ*=0.15 (s, 9H, Me_3Si), 2.00–2.10 (m, 1H, C*H*H-9), 2.34 (dm, *J*=ca. 17.1 Hz, 1H, C*H*H-9), 2.90–3.07 (m, 2H, CH_2-3), 3.42 (dm, *J*=ca. 18.3 Hz, 1H, NC*H*H), 4.16 (dq, *J*=11.5, 3.4 Hz, 1H, CH-9a), 5.06 (dm, *J*=18.3 Hz, 1H, NCH*H*), 5.69–5.76 (m, 1H, =CH-7), 5.76–5.83 (m, 1H, =CH-8), 6.02 (ddd, *J*=4.2, 3.2, 1.0 Hz, 1H, =CH-2); ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ*=−1.1, 32.9, 34.1, 41.7, 57.6, 124.8, 125.0, 131.1, 137.2, 166.1; GC–MS (70 eV): 221 (79) [M^+], 220 (100), 206 (12), 152 (14), 148 (23), 124 (23), 100 (34), 73 (28); IR (film): *ν*=3036, 2960, 1666, 1644, 1468, 1444, 1404, 1296, 1254, 1116, 840, 760 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calculated for $C_{12}H_{20}NOSi$, 222.1314; found 222.1319.

*4.5.10. (±)-1-Chloro-3,6,9,9a-tetrahydroquinolizin-4-one (**9j**).* Colourless oil (175 mg, 95% yield). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate, 1:1 then 4:6); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): *δ*=2.10–2.22 (m, 1H, C*H*H-9), 2.73 (dm, *J*=17.1 Hz, 1H, C*H*H-9), 3.08 (t, *J*=3.9 Hz, 2H, CH_2-3), 3.47 (dm, *J*=18.6 Hz, 1H, NC*H*H), 4.08 (dq, *J*=11.2, 3.9 Hz, 1H, CH-9a), 4.96 (dm, *J*=18.6 Hz, 1H, NCH*H*), 5.73 (dm, *J*=10.6 Hz, 1H, =CH-8), 5.81–5.85 (m, 1H, =CH-7), 5.86 (td, *J*=3.7, 0.7 Hz, 1H, =CH-2); ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ*=31.9, 32.4, 42.2, 57.9, 119.6, 123.9, 124.3, 128.0, 164.5; GC–MS (70 eV): 185 (31) [M^++2], 184 (M+1, 21), 183 (M^+, 100), 148 (14), 120 (15), 105 (14), 101 (18), 54 (41), 39 (16); IR (film): *ν*=3040, 2892, 2852, 1666, 1644, 1464, 1420, 1408, 1320, 1248, 1108, 1020, 968, 932, 884, 820, 720 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calculated for $C_9H_{11}ClNO$, 184.0529; found 184.0534.

*4.5.11. (±)-1-Phenyl-3,6,9,9a-tetrahydroquinolizin-4-one (**9k**).* Pale green oil (175 mg, 78% yield). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate, 1:1 then 4:6); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): *δ*=1.99–2.10 (m, 1H, C*H*H-9), 2.18–2.27 (m, 1H, C*H*H-9), 3.17 (q, *J*=3.6 Hz, 2H, CH_2-3), 3.56 (dm, *J*=ca. 18.5 Hz, 1H, NC*H*H), 4.61 (dq, *J*=11.2, 3.6 Hz, 1H, CH-9a), 5.08 (dm, *J*=ca. 18.5 Hz, 1H, NCH*H*), 5.70–5.78 (m, 2H, =CH-7, =CH-8), 5.89 (t, *J*=3.6 Hz, 1H, =CH-2), 7.29–7.42 (m, 5H, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ*=32.1, 32.7, 42.1, 56.4, 119.1, 124.6, 124.7, 126.3, 127.9, 128.7, 136.3, 138.2, 166.0; GC–MS (70 eV): 225 (100) [M^+], 224 (54), 196 (7), 182 (7), 171 (9), 156 (8), 143 (53), 134 (14), 129 (19), 128 (20), 115 (57), 102 (8), 91 (10), 77 (10), 63 (8), 51 (10), 39 (13); IR (film): *ν*=3036, 2892, 2848, 1660, 1640, 1472, 1444, 1406, 1332, 1302, 1252, 1208, 1104, 830, 764, 732, 700, 664 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calculated for $C_{15}H_{16}NO$, 226.1232; found 226.1230.

*4.5.12. (±)-1-(4-Fluorophenyl)-3,6,9,9a-tetrahydroquinolizin-4-one (**9l**).* White solid (211 mg, 87% yield). Mp 124–126 °C (*n*-hexane). The crude product was purified by column chromatography (SiO_2, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): *δ*=1.98–2.09 (m, 1H, C*H*H-9a), 2.15–2.24 (m, 1H, C*H*H-9a), 3.08–3.24 (m, 2H, CH_2-3), 3.55 (dm, *J*=ca. 19 Hz, 1H, NC*H*H), 4.56 (dq, *J*=11.2, 3.8 Hz, 1H, CH-9a), 5.09 (dm, *J*=ca. 19 Hz, 1H, NCH*H*), 5.72–5.77 (m, 2H, =CH-7, =CH-7), 5.85 (ddd, *J*=4.0, 3.2, 0.8 Hz, 1H, =CH-2), 7.02–7.09 (m, 2H, ArF), 7.26–7.32 (m, 2H, ArF); ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ*=32.1, 32.7, 42.1, 56.5, 115.6 (d, *J*=22.0 Hz), 119.3, 124.6, 124.6, 128.0 (d, *J*=7.3 Hz), 134.3 (d, *J*=2.9 Hz), 135.4, 162.4 (d, *J*=247.4 Hz), 167.8; GC–MS (70 eV): 243 (100) [M^+], 242 (50), 161 (59), 147 (14), 134 (27), 133 (42); IR (KBr pellet): 3088, 2888, 2848, 1668, 1634, 1510, 1468, 1448, 1400, 1328, 1300, 1250, 1220, 1164, 1144, 1104, 1056, 964, 850, 820, 812, 756, 672 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calculated for $C_{15}H_{15}FNO$, 244.1138; found 244.1138.

*4.5.13. (±)-1-Phenylsulfanyl-3,6,9,9a-tetrahydroquinolizin-4-one (**9m**).* Colourless oil (214 mg, 83% yield). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): *δ*=2.08–2.19 (m, 1H, C*H*H-9), 2.72 (dm, *J*=ca. 17.1 Hz, 1H, C*H*H-9), 3.04–3.20 (m, 2H, CH_2-3), 3.38 (dm, *J*=18.3 Hz, 1H, NC*H*H), 3.96 (dq, *J*=11.2, 3.7 Hz, 1H, CH-9a), 4.98 (dm, *J*=18.3 Hz, 1H, NCH*H*), 5.65 (dm, *J*=10.0 Hz, 1H, =CH), 5.74–5.81 (m, 1H, =CH), 6.04 (ddd, *J*=ca. 4.1, 3.2, 0.7 Hz, 1H, =CH-2), 7.24–7.39 (m, 5H, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ*=32.8, 33.1, 42.1, 56.8, 124.4, 124.6, 127.4, 127.5, 129.4, 130.4, 130.7, 133.1, 165.2; GC–MS (70 eV): 257 (100) [M^+], 224 (9), 203 (13), 174 (9), 161 (14), 148 (21), 104 (14), 71 (10); IR (film): *ν*=3040, 2896, 2844, 1664, 1642, 1476, 1440, 1248, 1110, 746, 692, 692 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calculated for $C_{15}H_{16}NOS$, 258.0953; found 258.0945.

*4.5.14. (±)-7-Methyl-3,6,9,9a-tetrahydroquinolizin-4-one (**9o**).* Colourless oil (129 mg, 79% yield). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate, 6:4 then 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): *δ*=1.71 (t, *J*=1.2 Hz, 3H, 7-CH_3), 2.00–2.12 (m, 1H, C*H*H-9), 2.18–2.28 (m, 1H, C*H*H-9), 3.00 (t, *J*=2.3 Hz, 2H, CH_2-3), 3.38 (d, *J*=18.8 Hz, 1H, NC*H*H), 3.95–4.05 (m, 1H, CH-9a), 4.76 (d, *J*=18.8 Hz, 1H, NCH*H*), 5.47–5.52 (m, 1H, =CH-8), 5.67–5.77 (m, 2H, =CH-1, =CH-2); ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ*=20.5, 31.9, 33.4, 45.3, 54.0, 118.5, 121.1, 125.0, 131.6, 166.3; GC–MS (70 eV): 163 (100) [M^+], 162 (39), 148 (13), 134 (12), 120 (11), 96 (40), 68 (31), 67 (35), 53 (11), 41 (13), 39 (16); IR (thin film): *ν*=3040, 2972, 2912, 2836, 1676, 1646, 1460, 1408, 1334, 1248, 1174, 1152, 1072, 956, 832, 798, 732, 694 cm^{-1}; HRMS (ESI-TOF): *m*/*z* [M^++H] calcd for $C_{10}H_{14}NO$, 164.1075; found 164.1073.

*4.5.15. (±)-1-Chloro-7-methyl-3,6,9,9a-tetrahydroquinolizin-4-one (**9p**).* Colourless oil (184 mg, 93% yield). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): *δ*=1.70–1.73 (m, 3H, 7-CH_3), 2.05–2.17 (m, 1H, C*H*H-9), 2.62–2.72 (m, 1H, C*H*H-9), 3.08 (td, *J*=3.9, 0.8 Hz, 2H, CH_2-3), 3.36 (d, *J*=18.1 Hz, 1H, NC*H*H), 4.01 (dq, *J*=11.3, 3.9 Hz, 1H, CH-9a), 4.81 (dsxt, *J*=18.1, 1.0 Hz, 1H, NCH*H*), 5.53 (dquint, *J*=6.1, 1.7 Hz, 1H, =CH-8), 5.85 (td, *J*=3.9, 0.9 Hz, 1H, =CH-2); ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ*=20.3, 31.8, 32.5, 45.7, 57.8, 118.2, 119.4, 128.1, 131.5, 164.5; GC–MS (70 eV): 199 (34) [M+2], 198 (18) [M+1], 197 [M^+], 182 (12), 130 (21), 68 (61), 67 (44), 53 (14), 39 (20); IR (thin film): *ν*=2972, 2932, 2840, 1682, 1644, 1460, 1408, 1328, 1312, 1300, 1246, 1202, 1104, 1022, 984, 956, 894, 836, 816, 662, 638 cm^{-1}; HRMS (ESI-TOF): *m*/*z* [M^++H] calculated $C_{10}H_{13}ClNO$, 198.0686; found 198.0676.

*4.5.16. (±)-7-Phenyl-3,6,9,9a-tetrahydroquinolizin-4-one (**9r**).* Pale green oil (180 mg, 80% yield). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): *δ*=2.24–2.34 (m, 1H, C*H*H-9), 2.44–2.52 (dm, 1H, C*H*H-9), 3.00–3.09 (m, 2H, CH_2-3), 3.79 (dm, *J*=17.8 Hz, 1H, NC*H*H), 4.09–4.17 (m, 1H, CH-9a), 5.42 (dt, *J*=17.8, 1.4 Hz, 1H, NCH*H*), 5.74–5.82 (m, 2H, =CH-1, =CH-2), 6.17 (dq, *J*=6.1, 2.0 Hz, 1H, =CH-8), 7.26–7.31 (m, 1H, C_6H_5), 7.32–7.37 (m, 2H, C_6H_5), 7.39–7.44 (m, 2H, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ*=31.9, 34.0, 43.2, 53.9, 120.9, 121.4, 124.8, 125.2, 127.7, 128.5, 134.7, 138.5, 166.4; GC–MS (70 eV): 225 (83) [M^+], 130 (100), 129 (96), 115 (49), 102 (10), 91 (14), 77 (12), 51 (15), 39 (12); IR (film): *ν*=3044,

2888, 2844, 1658, 1638, 1462, 1444, 1328, 1254, 1162, 840, 756, 696 cm^{-1}. HRMS (ESI-TOF): *m/z* [M^++H] calculated for $C_{15}H_{16}NO$, 226.1232; found 226.1223.

*4.5.17. (±)-1-Chloro-7-phenyl-3,6,9,9a-tetrahydroquinolizin-4-one (**9s**).* Colourless solid (237 mg, 91% yield). Mp 97–99 °C (*n*-hexane/ethyl/acetate). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate, 6:4 then 1:1 then 4:6); ^1H NMR (400 MHz, $CDCl_3$, 23 °C): δ=2.34 (dddd, *J*=17.4, 11.3, 6.3, 2.8 Hz, 1H, C*H*H-9), 2.92 (ddt, *J*=17.4, 6.2, 2.5 Hz, 1H, C*H*H-9), 3.14 (t, *J*=3.8 Hz, 2H, CH_2-3), 3.77 (dm, *J*=17.8 Hz, 1H, NC*H*H), 4.15 (dq, *J*=11.3, ca. 3.7 Hz, 1H, CH-9a), 5.46 (dt, *J*=17.8, 1.2 Hz, 1H, NCH*H*), 5.90 (td, *J*=3.8, 0.7 Hz, 1H, =CH-2), 6.17–6.21 (m, 1H, =CH-8), 7.27–7.43 (m, 5H, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=32.4, 32.6, 43.6, 57.7, 119.6, 120.5, 125.2, 127.9, 127.9, 128.6, 134.6, 138.1, 164.6; GC–MS (70 eV): 261 (19) [M^++2] 260 (10) [M^++1] 259 (M+, 52), 130 (100), 129 (78), 115 (46), 102 (11), 91 (12), 77 (16), 51 (14), 39 (12); IR (KBr pellet): ν=3056, 3024, 2956, 2888, 1660, 1640, 1404, 1328, 1252, 1020, 974, 892, 844, 812, 800, 756, 696, 654 cm^{-1}. HRMS (ESI-TOF): *m/z* [M^++H] calcd for $C_{15}H_{15}ClNO$, 260.0842; found 260.0835.

*4.5.18. (±)-1,7-Diphenyl-3,6,9,9a-tetrahydroquinolizin-4-one (**9t**).* Pale yellow oil (198 mg, 66% yield). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate 1:1 then 4:6); ^1H NMR (400 MHz, $CDCl_3$, 23 °C): δ=2.16–2.27 (m, 1H, C*H*H-9), 2.43 (dquint, *J*=17.6, 2.9 Hz, 1H, C*H*H-9), 3.14–3.30 (m, 2H, CH_2-3), 3.86 (br d, *J*=17.6 Hz, 1H, NC*H*H), 4.68 (dq, *J*=11.5, 3.9 Hz, 1H, CH-9a), 5.60 (dt, *J*=17.8, 1.5 Hz, 1H, NCH*H*), 5.94 (t, *J*=3.7 Hz, 1H, =CH-2), 6.11 (dq, *J*=6.1, 1.7 Hz, 1H, =CH-8), 7.25–7.44 (m, 10H, 2×C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=32.3, 33.2, 43.5, 56.1, 119.1, 121.5, 125.2, 126.3, 127.8, 128.0, 128.5, 128.8, 134.8, 136.1, 138.1, 138.4, 166.0; GC–MS (70 eV): 301 (98) [M^+], 130 (100), 129 (76), 115 (65), 102 (10), 91 (13), 77 (11); IR (thin film): ν=3056, 3032, 2888, 1656, 1638, 1496, 1472, 1444, 1406, 1304, 1254, 1198, 1066, 1020, 910, 844, 758, 730, 698 cm^{-1}. HRMS (ESI-TOF): *m/z* [M^++H] calcd for $C_{21}H_{20}NO$, 302.1545; found 302.1551.

*4.5.19. (±)-7-Phenyl-1-phenylsulfanyl-3,6,9,9a-tetrahydroquinolizin-4-one (**9u**).* Colourless solid (254 mg, 76% yield). Mp 158–160 °C (*n*-hexane/ethyl acetate). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate 1:1 then 4:6); ^1H NMR (400 MHz, $CDCl_3$, 23 °C): δ=2.25–2.36 (m, 1H, C*H*H-9), 2.90 (dm, *J*=17.5 Hz, 1H, C*H*H-9), 3.09–3.26 (m, 2H, CH_2-3), 3.68 (br d, *J*=17.5 Hz, 1H, NC*H*H), 4.02 (dq, *J*=11.5, 3.5 Hz, 1H, CH-9a), 5.49 (dt, *J*=17.6, 1.2 Hz, 1H, NCH*H*), 6.08 (dd, *J*=3.8, 3.5 Hz, 1H, =CH-2), 6.13 (dq, *J*=6.1, 1.8 Hz, 1H, =CH-8), 7.23–7.42 (m, 10H, 2×C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=32.2, 33.3, 43.5, 56.5, 121.2, 125.2, 127.4, 127.6, 127.8, 128.5, 129.4, 130.2, 130.7, 133.0, 134.6, 138.2, 165.3; GC–MS (70 eV): 333 (100) [M^+], 224 (10), 203 (34), 130 (52), 129 (40), 128 (20), 115 (29), 104 (11), 91 (11), 77 (10); IR (pellet KBr): ν=3036, 2928, 1660, 1640, 1584, 1496, 1468, 1442, 1424, 1392, 1356, 1330, 1260, 1190, 1024, 844, 752, 736, 690 cm^{-1}. HRMS (ESI-TOF): *m/z* [M^++H] calcd for $C_{21}H_{20}NOS$, 334.1266; found 334.1266.

*4.5.20. (±)-6,7,10,10a-Tetrahydro-3H-pyrido[1,2-a]azepin-4-one (**9v**).* Colourless oil (134 mg, 82% yield). The crude product was purified by column chromatography (SiO_2, diethyl ether); ^1H NMR (400 MHz, $CDCl_3$, 23 °C): δ=2.10–2.21 (m, 1H, C*H*H-10), 2.29–2.46 (m, 3H, CH_2-7, C*H*H-10), 2.79 (ddd, *J*=13.5, 10.1, 2.9 Hz, 1H, NC*H*H), 2.97–3.01 (m, 2H, CH_2-3), 3.97–4.04 (m, 1H, CH-10a), 4.53 (ddd, *J*=13.5, 4.9, 3.9 Hz, 1H, NCH*H*), 5.68–5.81 (m, 3H, =CH-1, =CH-2, =CH-8), 5.85–5.93 (m, 1H, =CH-9); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=28.6, 31.7, 37.4, 46.4, 59.4, 121.6, 126.6, 127.7, 131.4, 168.2; GC–MS (70 eV): 163 (8) [M^+], 109 (26), 96 (63), 81 (48), 80 (100), 68 (26), 53 (16), 44 (22), 39 (26); IR (film): ν=3016, 2920, 2908, 1640, 1468, 1432, 1368, 1322, 718 cm^{-1}. HRMS (ESI-TOF): *m/z* [M^++H] calcd for $C_{10}H_{14}NO$, 164.1075; found 164.1069.

*4.5.21. (±)-1-Phenyl-6,7,10,10a-tetrahydro-3H-pyrido[1,2-a]azepin-4-one (**9w**).* Pale yellow solid (198 mg, 83% yield). Mp 101–103 °C (*n*-hexane/ethyl acetate). The crude product was purified by column chromatography (SiO_2, diethyl ether); ^1H NMR (400 MHz, $CDCl_3$, 23 °C): δ=2.14–2.26 (m, 1H, C*H*H-10), 2.31–2.41 (m, 2H, C*H*H-10, C*H*H-7), 2.45–2.57 (m, 1H, C*H*H-7), 2.77 (ddd, *J*=13.4, 11.2, 2.4 Hz, 1H, NC*H*H), 3.09–3.25 (m, 2H, CH_2-3), 4.40 (dq, *J*=10.9, 2.1 Hz, 1H, CH-10a), 4.65 (dt, *J*=13.4, 4.0 Hz, 1H, NCH*H*), 5.69 (ddt, *J*=11.4, 8.1, 2.9 Hz, 1H, =CH-8), 5.91 (ddt, *J*=11.4, 7.8, 3.2 Hz, 1H, =CH-9), 6.03 (dd, *J*=4.9, 3.1 Hz, 1H, =CH-2), 7.29–7.42 (m, 5H, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=29.1, 33.0, 36.8, 46.7, 61.7, 119.3, 125.9, 127.9, 128.3, 128.8, 131.5, 137.7, 138.4, 167.3; GC–MS (70 eV): 239 (25) [M^+], 185 (22), 172 (24), 171 (90), 157 (26), 156 (100), 128 (32), 115 (22); IR (KBr pellet): ν=3060, 3008, 2916, 1648, 1492, 1472, 1428, 1368, 1348, 1292, 1270, 1176, 1056, 960, 932, 836, 760, 696 cm^{-1}. HRMS (ESI-TOF): *m/z* [M^++H] calcd for $C_{16}H_{18}NO$, 240.1388; found 240.1383.

*4.5.22. (±)-1-Phenylsulfanyl-6,7,10,10a-tetrahydro-3H-pyrido-[1,2-a]azepin-4-one (**9x**).* White solid (246 mg, 91% yield). Mp 111–113 °C (*n*-hexane). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate, 1:1); ^1H NMR (400 MHz, $CDCl_3$, 23 °C): δ=2.16–2.28 (m, 2H, C*H*H-7, C*H*H-10), 2.37–2.48 (m, 1H, C*H*H-10), 2.53 (ddd, *J*=12.8, 11.3, 2.2 Hz, 1H, NC*H*H), 2.83 (ddd, *J*=16.6, 7.8, 2.2 Hz, 1H, C*H*H-7), 3.07 (dt, *J*=21.7, 2.7 Hz, 1H, C*H*H-3), 3.16 (dd, *J*=21.7, 5.1 Hz, 1H, C*H*H-3), 3.73 (dq, *J*=11.1, 1.3 Hz, 1H, CH-10a), 4.51 (dt, *J*=12.9, 3.9 Hz, 1H, NCH*H*), 5.69–5.76 (m, 1H, =CH-9), 5.80–5.87 (m, 1H, =CH-8), 6.03 (dd, *J*=5.1, 2.7 Hz, 1H, =CH-2), 7.24–7.27 (m, 5H, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=28.9, 34.0, 36.4, 46.4, 62.0, 127.4, 127.5, 128.0, 129.4, 130.3, 131.2, 132.5, 133.4, 166.8; GC–MS (70 eV): 271 (64) [M^+], 217 (12), 203 (92), 188 (100), 162 (17), 160 (20), 109 (14), 80 (11), 67 (11); IR (KBr pellet): ν=3056, 3016, 2920, 2880, 1648, 1580, 1474, 1428, 1364, 1264, 1172, 1024, 932, 828, 736, 716, 692 cm^{-1}; HRMS (ESI-TOF): *m/z* [M^++H] calculated for $C_{16}H_{18}NOS$, 272.1109; found 272.1110.

*4.5.23. (±)-3,6,7,8,11,11a-Hexahydropyrido[1,2-a]azocin-4-one (+10% trans) (**9y**).* Colourless oil (133 mg, 75% yield). The crude product was purified by column chromatography (SiO_2, diethyl ether); ^1H NMR (400 MHz, toluene-d_8, 23 °C): δ=0.83–0.93 (m, 1H, C*H*H-7), 1.51–1.61 (m, 2H, C*H*H-8, C*H*H-11), 1.99 (ddd, *J*=13.3, 12.2, 3.4 Hz, 1H, NC*H*H), 2.17–2.29 (m, 1H, C*H*H-7), 2.40 (td, *J*=3.5, 1.9 Hz, 2H, CH_2-3), 3.00–3.07 (m, 1H, CH-11a), 3.85 (ddd, *J*=13.3, 4.0, 2.6 Hz, 1H, NCH*H*), 4.86 (ddt, *J*=10.0, 3.8, 2.0 Hz, 1H, =CH), 5.01 (dtd, *J*=10.0, 3.4, 1.2 Hz, 1H, =CH), 5.16 (td, *J*=9.5, 7.0 Hz, 1H, =CH), 5.36 (td, *J*=9.5, 7.2 Hz, 1H, =CH); ^{13}C NMR (100.6 MHz, toluene-d_8): δ=23.2, 25.2, 30.9, 32.5, 46.2, 60.4, 120.9, 124.8, 125.3, 132.3, 165.1; GC–MS (70 eV): 177 (16) [M^+], 176 (21), 122 (31), 109 (100), 96 (33), 82 (22), 81 (40), 80 (31), 67 (39), 53 (11), 41 (16), 39 (16); IR (film): ν=3020, 2932, 1642, 1468, 1430, 1408, 1364, 1334, 818, 764, 740, 714 cm^{-1}. HRMS (ESI-TOF): *m/z* [M^++H] calculated for $C_{11}H_{16}NO$, 178.1232; found 178.1234.

*4.5.24. (±)-2,9,9-Trimethyl-3,6,9,9a-tetrahydroquinolizin-4-one (**13**).* Colourless oil (85.6 mg, 90% yield[¶]). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate, 6:4 then 1:1); ^1H NMR (400 MHz, $CDCl_3$, 23 °C): δ=0.83 (s, 3H, 9-

[¶] From the 1:1 mixture of compounds **12a** and **12b**.

CH_3), 1.06 (s, 3H, 9-CH_3), 1.78 (3H, s, 2-CH_3), 2.84 (dm, *J*=ca. 21.7 Hz, 1H, C*H*H-3), 2.95 (dm, *J*=ca. 21.6 Hz, 1H, C*H*H-3), 3.39 (d, *J*=18.4 Hz, 1H, NC*H*H), 3.76–3.81 (m, 1H, CH-9a), 4.90 (d, *J*=18.4 Hz, 1H, NCH*H*), 5.51 (br s, 1H, =CH-1), 5.55–5.57 (m, 2H, =CH-7, CH-8); ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ*=21.8, 22.2, 25.8, 36.4, 38.1, 41.7, 63.5, 115.7, 121.0, 131.7, 136.9, 167.0 (C-4); GC–MS (70 eV): 191 (12) [M^+], 110 (100), 92 (10), 82 (33), 67 (38), 53 (10), 41 (14), 39 (12); IR (film): *ν*=2964, 1648 br, 1262, 1100 br, 1020 br, 804 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calculated for $C_{12}H_{18}NO$, 192.1388; found 192.1380.

*4.5.25. (±)-1′-Phenyl-4′,6′,9′,9a′-tetrahydrospiro(cyclopentane-1,3′-quinolizin)-3-en-4′-one (**15a**).* Colourless oil (173 mg, 62% yield). The crude product was purified by column chromatography (SiO_2, *n*-hexane: ethyl acetate, 7:3 then 6:4); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): *δ*=1.93–2.04 (m, 1H, C*H*H-9′), 2.20–2.29 (m, 1H, C*H*H-9′), 2.35 (dq, *J*=16.2, 2.1 Hz, 1H, C*H*H), 2.45 (dq, *J*=16.5, 2.1 Hz, 1H, C*H*H), 3.02 (dquint, *J*=16.5, 2.2 Hz, 1H, C*H*H), 3.30 (dquint, *J*=16.5, 2.2 Hz, 1H, C*H*H), 3.59 (dm, *J*=18.0 Hz, 1H, NC*H*H), 4.61 (dd, *J*=11.2, 3.4 Hz, 1H, CH-9a′), 5.09 (br d, *J*=18.0 Hz, 1H), 5.62–5.67 (m, 1H, =CH), 5.68–5.72 (m, 1H, CH), 5.74 and 5.75 (twos, 2H, =CH-7′, =CH-8′), 5.96 (s, 1H, =CH-2′), 7.29–7.38 (m, 5H, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ*=33.4, 42.7, 46.1, 47.2, 48.5, 56.2, 124.6, 125.9, 126.3, 127.3, 127.3, 128.7, 128.8, 130.0, 132.5, 138.0, 172.4; GC–MS (70 eV): 277 (100) [M^+], 223 (56), 222 (70), 208 (25), 194 (67), 165 (19), 152 (10), 115 (10); IR (thin film, ATR): *ν*=3054, 3032, 2912, 2842, 1660, 1631, 1462, 1443, 1300, 1234, 1206, 948, 908, 760, 727, 698, 656 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calculated $C_{19}H_{20}NO$, 278.1545; found 278.1552.

*4.5.26. (±)-1′-Phenyl-6′,7′,10′,10a′-tetrahydrospiro(cyclopentane-1,3′-pyrido[1,2-a]azepin)-3-en-4′-one (**15b**).* White solid (256 mg, 88% yield). Mp 115–117 °C (*n*-hexane). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate, 7:3 then 6:4); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): *δ*=2.07–2.17 (m, 1H, C*H*H-10′), 2.31–2.54 (m, 5H, C*H*H-10′, CH_2-7′, 2×C*H*H), 2.79 (ddd, *J*=13.3, 11.2, 2.5 Hz, 1H, NC*H*H), 3.00 (dquint, *J*=16.1, 2.4 Hz, 1H, C*H*H), 3.38 (dquint, *J*=16.5, 2.5 Hz, 1H, C*H*H), 4.42 (dd, *J*=10.7, 2.0 Hz, 1H, CH-10a′), 4.66 (ddd, *J*=13.3, 4.9, 3.7 Hz, 1H, NCH*H*), 5.62–5.76 (m, 3H, 3×=CH), 5.90–5.97 (m, 1H, =CH), 6.06 (s, 1H, =CH-2′), 7.28–7.42 (m, 5H, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ*=29.0, 38.1, 45.7, 47.0, 47.9, 48.9, 61.4, 126.1, 127.1, 127.8, 128.3, 128.7, 129.1, 130.9, 132.0, 134.9, 137.8, 173.2; GC–MS (70 eV): 291 (100) [M^+], 274 (19), 262 (12), 237 (88), 236 (94), 222 (26), 209 (31), 208 (81), 194 (32), 178 (16), 165 (27), 152 (15), 128 (13), 115 (21), 77 (12), 67 (12); IR (KBr pellet): *ν*=3060, 3020, 2920, 2860, 1630, 1600, 1472, 1428, 1374, 1344, 1336, 1252, 1220, 952, 936, 876, 766, 720, 702 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calculated $C_{20}H_{22}NO$, 292.1701; found 292.1700.

*4.5.27. (±)-1′-Phenylsulfanyl-4′,6′,9′,9a′-tetrahydrospiro(cyclopentane-1,3′-quinolizin)-3-en-4′-one (**15c**).* Colourless oil (320 mg, 88% yield). The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate, 7:3 then 6:4); ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): *δ*=2.02–2.12 (m, 1H, C*H*H-9′), 2.38 (dm, *J*=ca. 16.4 Hz, 2H, 2×C*H*H), 2.73 (dm, *J*=16.8 Hz, 1H, C*H*H-9′), 2.94 (dquint, *J*=16.1, 2.6 Hz, 1H, C*H*H), 3.31 (dquint, *J*=16.4, 2.4 Hz, 1H, C*H*H), 3.39 (dsxt, *J*=18.3, 2.20 Hz, 1H, NC*H*H), 3.93 (dd, *J*=11.2, 3.4 Hz, 1H, CH-9a′), 4.99 (dm, *J*=18.3 Hz, 1H, NCH*H*), 5.58–5.62 (m, 1H, =CH), 5.63–5.71 (m, 2H, 2×=CH), 5.73–5.80 (m, 1H, =CH), 6.19 (s, 1H, =CH-2′), 7.23–7.36 (m, 5H, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ*=33.3, 42.7, 45.7, 47.7, 47.9, 48.7, 56.7, 124.4, 124.6, 126.8, 127.2, 128.6, 129.3, 129.9, 133.7, 139.4, 171.6; GC–MS (70 eV): 309 (100) [M^+], 255 (98), 240 (17), 226 (48), 200 (28), 145 (16), 128 (19), 117 (18), 91 (16), 77 (17), 65 (14); IR (thin film, ATR): 3055, 2913, 2842, 1661, 1635, 1580, 1475, 1440, 1334, 1294, 1230, 1205, 1024, 946, 910, 726, 690, 652 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M^++H] calculated $C_{19}H_{20}NOS$, 310.1266; found 310.1254.

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Supplementary data

Experimental procedures and spectroscopic data for **3**, some 2-methoxypyridines and NH pyridin-2(1*H*)-ones as precursors of **3** as well as for **7**, **8g**, **10a**, **12a**, **13**, **14**. ^{1}H and ^{13}C NMR spectra of compounds **3** (except **3a**), **7**, **8a**, **8b**, **8c**, **8g**, **8z**, **8ab**, **9**, **10a**, **12a**, **13**, **14**, **15**, ^{1}H,^{1}H NOESY spectra of **9f**, **9g**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.09.043.

References and notes

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