Microwave-Assisted Domino Hydroformylation/Cyclization Reactions: Scope and Limitations

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To the memory of Charles Mioskowski

Abstract: Hydroformylation of alkenes can be carried out in short time and with low syngas pressure under microwave (MW) dielectric heating. Alkenes, carrying O-, N-, or C-nucleophilic fragments, can be designed for domino reactions, mainly cyclocondensations. Allyl and homoallyl alcohols are excellent substrates for cyclizative hydroformylation to lactols under MW heating. In the presence of NaOAc as an additional nucleophile, a domino reaction occurs giving 2-acetoxytetrahydrofurans, suitable to introduce a C-nucleophile on tetrahydrofuran rings through an oxocarbenium ion. The synthesis of the furanopiperidine substructure of cyclopamine is described as an application. With alkene amides, the domino process collapsed to a transient acyliminium ion that further cyclized with an additional C-nucleophile. To perform domino hydroformylation Pictet–Spengler or aza-Sakurai reactions, an autoclave under conventional heating is essential. Syntheses of (±)-epilupinine and of a homoberberine alkaloid are reported to illustrate each sequence. Although apparently more versatile, hydroformylation of alkenes using MW heating is sensitive to the nature of the nucleophiles present in the substrates, evidencing that the conventional heating process cannot be completely replaced by MW irradiation.

Key words: domino reaction, heterocycles, nucleophilic addition, cyclization, hemiacetals, Pictet–Spengler reaction

The use of microwaves (MWs) to heat organic reactions has attracted considerable attention during the last 20 years.[1] This technique allows to reduce markedly the time required for a chemical process, the formation of by-products, and by the way improves yields and purity. Although MW irradiation is an alternative to conventional heating, the use of this technology has launched a new concept in synthetic technologies, as transmission and absorption of energy are different compared to conventional thermal heating. As MWs generate temperature profiles different from traditional heating, in some cases kinetic control can be achieved.[2] Moreover, several reactions have been reported in which the chemo-, regio- and stereoselectivity changed under MW conditions in comparison to conventional heating.[3] Over the years the importance taken by MW-assisted reactions in organic synthesis can be easily measured by the increasing number of scientific publications (including patents). As most of the reactors for MWs have been designed to resist the pressure internally generated by the solvent, they can be considered as small autoclaves adjustable to run reactions with gaseous reagents.

Since its discovery in 1938, hydroformylation of olefins has evolved as one of the industrially most important processes, which relies on homogeneous catalysis.[4] Recently we reported a general procedure for the MW-assisted hydroformylation of terminal olefins in adapting the 80 mL vial of a MW oven.[5] This glass vial, tested for resisting up to 1700 kPa, is connected to an external pressure controlling system equipped with a valve that allows to control the inlet and outlet of the gas during the pressurization or depressurization steps. From this experience, CEM has designed a kit for gas addition adapted to its Discover synthesis apparatus.[6] Moreover, other suppliers of MW devices provide PTFE vials that can be filled with pressurized gas and safely submitted to MW dielectric heating.[7]

The combination of hydroformylation MW heating revealed several advantages over the classical autoclave process: the reaction time and temperature were considerably reduced, and improvements in the selectivity were observed in some cases.[8] Moreover, as the hydroformylation can be run in small flasks, the amount of H_2 and CO wasted at the end of the reaction can be reduced to a minimum, a real atom-economic hydroformylation is at hand.[9] Another advantage of MWs is the possibility to promote the integration of the hydroformylation products in domino reactions. Recently, several applications of domino processes initiated by the hydroformylation of alkenyl substrates have been reported.[10]

In order to investigate the potential of MW dielectric heating in domino hydroformylation/cyclization processes, we report here on the transformation of terminal olefins by using extensively MW-assisted hydroformylation and comparing it with the traditional autoclave pressurized process. The unsaturated substrates were designed to contain various O, N, or C nucleophiles. Therefore, once the aldehydes are formed, domino sequences can take place towards the production of heterocycles of interest. Although MW heating was more versatile, the nature of the

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nucleophile subordinated the choice of the best heating technology, demonstrating that the conventional heating can be sometimes preferred to MWs.

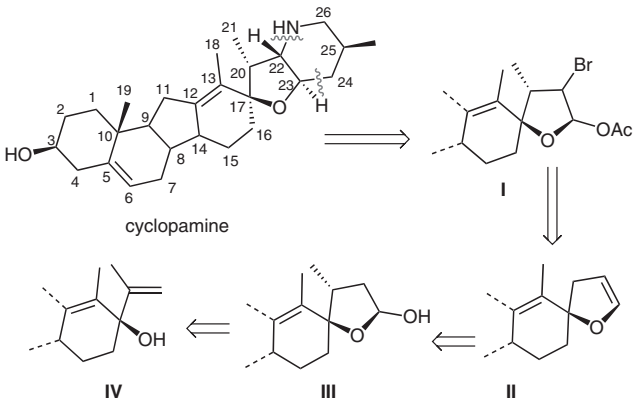
Oxygen as the Nucleophile

Decades ago hydroformylation of allyl and homoallyl alcohols has been investigated as a rapid method to generate five- and six-membered hemiacetals originating from spontaneous cyclization of the transient linear hydroxy aldehyde.[10h] Moreover, the versatile reactivity of cyclic hemiacetals points them out as useful intermediates in the synthesis of many valuable compounds.[11]

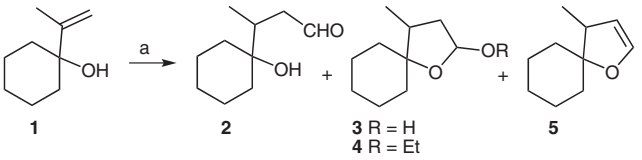
In contrast to extensive efforts devoted to study the influence of achiral or chiral catalysts on this reaction,[12] relatively few substrates have been investigated. We came across the possibility to use the allyl alcohol hydroformylation to prepare substituted tetrahydrofurans within a project directed to the synthesis of the furanopiperidine substructure of cyclopamine, the most important component of the veratrum alkaloid family.[13]

Our retrosynthetic sequence was based on a disconnection at the level of C22 and C23 giving a spiro-tetrahydrofuran derivative with two leaving groups (structure **I** in Scheme 1). Dihydrofuran **II** and the cyclic hemiacetal **III** are the corresponding precursors that are accessible by hydroformylation of unsaturated alcohol **IV**. To establish the feasibility of this strategy, compound **1** was subjected to cyclizative hydroformylation, under different reaction conditions (Scheme 2). Although making the linear aldehyde **2** is crucial, the direct preparation of adducts **5** or **3** was our first goal. Different parameters were studied in order to maximize their yields (see Table 1 for the data). The reactions were performed inside a sealed pressurized vial using the gas kit, an available accessory of the Discovery microwave synthesis instrument.[6] $(PPh)_3Rh(CO)H$ and $Rh(CO)_2acac$ were used as precatalyst in the presence of various ligands such as Ph_3P, xantphos, or biphephos. Toluene, THF, and EtOH were the solvents of choice. The influence of temperature and additives such as ionic liquids was also investigated. The solvent had an influence in the products distribution. In toluene (in the presence of small amounts of [bmim][BF_4] in order to raise the temperature to 110 °C) the starting alcohol **1** was recovered after two hours of reaction (Table 1, entry 1). With THF, the hemiacetal **3** (as a 1:1 diastereomeric mixture) was formed in low yields (35%) together with the linear aldehyde **2** (Table 1, entry 2). The use of EtOH as the solvent increased the conversion of **1**, but acetal **4** (diastereomeric mixture) was the only isolated product (Table 1, entry 3). A temperature above 90 °C and a period of 3 hours were required to obtain a complete conversion.

At a lower temperature, the conversion of **1** required a longer time and the formation of many by-products was observed (Table 1, entry 6). At 110 °C in THF, the conversion of **1** was almost quantitative after 60 minutes, but lactol **3** was isolated only in 65% yield (Table 1, entry 7).



Scheme 1 Retrosynthetic proposal for the alkaloid substructure of cyclopamine



Scheme 2 *Reagents and conditions*: (a) H_2/CO (1:1), Rh (cat), ligand (see Table 1).

No remarkable effect was observed changing the Rh(I) source (Table 1, cf. entries 7 and 8), while, as expected, xantphos promoted the formation of the tetrahydrofuran derived from the linear aldehyde **2**, and biphephos gave poor results due to the high temperature required for the reaction (Table 1, entry 9). In the presence of Ph_3P, the only detectable product was the reduced 1-isopropylcyclohexanol (Table 1, entry 10). Exploring different reaction conditions in THF, we observed that the presence of a small amount of water increased the yields of **3** up to 92% after two cycles of 30 and 45 minutes, respectively (Table 1, entry 11). As previously observed, two irradiation cycles gave better results in terms of yields in respect to a single reaction cycle of overall 75 minutes. To induce the in situ conversion of **3** into **5**, the hydroformylation was repeated in the presence of acid additives, but no effect was observed (Table 1, entries 12 and 13). Analogously, elimination of EtOH from **4** under several acidic conditions gave unsatisfactory results.

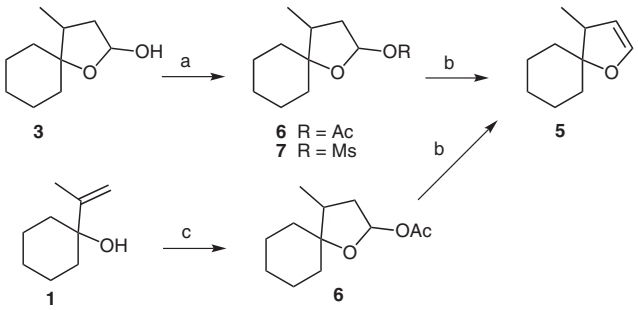
One approach to **5** was the transformation of **3** into the acetate **6** or mesylate **7** followed by pyridine mediated elimination (Scheme 3). Then, the possibility to transform directly alcohol **1** into the acetate **6** during the process of tandem hydroformylation/cyclization was explored. When running the reaction on **1** in THF under MW dielectric heating in the presence of $(PPh_3)_3Rh(CO)H$/xantphos as catalyst and a mixture of NaOAc/AcOH (1:1) as additive; the acetate **6** was obtained in good yields (Table 1, entry 14). This result was remarkable as 2-acetoxytetrahydrofurans are employed to generate five-membered ring oxocarbenium ions,[14] the ideal intermediates for the stereoselective introduction of nucleophiles in position 2 of a tetrahydrofuran ring.[15] The formation of these adducts

Table 1 Optimization of the Reaction Conditions for the Hydroformylation of **1**

Entry	Reaction conditions[a]	Products (yield, %)[b]
1	MW, toluene, [bmim][BF_4], 110 °C, 2 h, **A**	staring material
2	MW, THF, [bmim][BF_4], 110 °C, 2 h, **A**	**2** (10) + **3** (35)
3	MW, EtOH, 110 °C, 90 min, **A**	**4** (67)
4	MW, EtOH, PTSA, 110 °C, **A**	dec.
5	MW, THF, 90 °C, 3 h, **A**	**3** (55)
6	MW, THF, 60 °C, 5 h, **A**	**3** (40) + dec.
7	MW, THF, 110 °C, 1 h, **A**	**3** (65)
8	MW, THF, 110 °C, 1 h, **B**	**3** (62)
9	MW, THF 110 °C, 1 h, **C**	dec.
10	MW, THF, 110 °C, 1 h, **D**	–[c]
11	MW, THF–H_2O, 110 °C, 30 + 45 min, **A**	**3** (92)
12	MW, THF, PTSA, 110 °C, 1 h, **A**	dec.
13	MW, THF–H_2O–HCl, 110 °C, 1 h, **A**	dec.
14	MW, THF–H_2O, NaOAc, AcOH, 110 °C, 1 h, **A**	**6** (88)
15	autoclave, THF–H_2O, 110 °C, 12 h, **A**	**3** (48)
16	autoclave, THF–H_2O, 110 °C, 24 h, **E**	**3** (70)
17	autoclave, THF–H_2O, NaOAc, AcOH, 110 °C, 12 h, **A**	dec.

[a] **A**: (PPh_3)$_3$Rh(CO)H (0.01 equiv)/xantphos (0.04 equiv), H_2/CO 827 kPa; **B**: Rh(CO)$_2$acac (0.01 equiv)/xantphos (0.04 equiv), H_2/CO 827 kPa; **C**: (PPh_3)$_3$Rh(CO)H (0.01 equiv)/biphephos (0.04 equiv), H_2/CO 827 kPa; **D**: Rh(CO)$_2$acac (0.02 equiv)/Ph_3P (0.1 equiv), H_2/CO 827 kPa; **E**: Rh(CO)$_2$acac (0.01 equiv)/biphephos (0.04 equiv), H_2/CO 1240 kPa.
[b] dec. = decomposition products.
[c] Reduction of the double bond to form 1-isopropylcyclohexanol was observed.

directly during hydroformylation of allylic alcohols increases the synthetic value of the transformation.



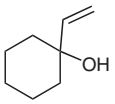
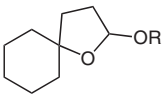
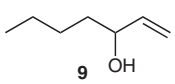
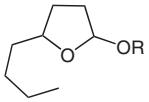
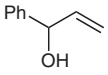
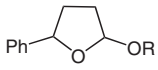
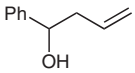
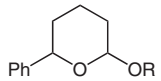
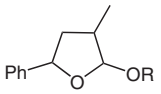
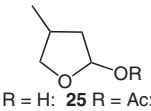
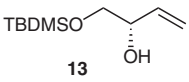
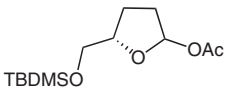
Scheme 3 *Reagents and conditions*: (a) Ac_2O, Et_3N, CH_2Cl_2, r.t., 80% or MsCl, Et_3N, CH_2Cl_2, 20 °C, 10 h, 60%; (b) pyridine, 80 °C, 6 h, 80%; (c) (PPh_3)$_3$Rh(CO)H (0.01 equiv)/xantphos (0.04 equiv), H_2/CO 827 kPa, THF, NaOAc/AcOH (1.5 equiv), MW, 110 °C, 60 min, 88%.

Conversely when compound **1** was submitted to hydroformylation in an autoclave under conditions comparable to the MW heating, the transformation into **3** was accomplished after 12 hours, but the product was isolated only in moderate yield (48%). However, working with Rh(CO)$_2$acac/biphephos at 60 °C for 24 hours, the yield of **3** could be increased to 70% (Table 1, entries 15,16). Attempts to transform **1** into **6** with a mixture of NaOAc/AcOH in THF in an autoclave gave mainly decomposition products (Table 1, entry 17).

The MW-assisted hydroformylation in THF was applied to different allyl alcohols. Varying the additive from H_2O to EtOH or NaOAc/AcOH it was possible to obtain hemiacetals, ethyl acetals, or the corresponding acetates in good to acceptable yields (Table 2).

The reaction gave the expected products with aliphatic and aromatic alcohols (Table 2, entries 1–3) and also with homoallylic alcohols. With alcohol **11**, the 2-hydroxytetrahydropyran **23a** was isolated together with small amounts of the tetrahydrofuran **23b** originating from the formation of the branched aldehyde during hydroformylation (Table 2, entry 4). In our hands, it was the only case where a branched aldehyde (or its cyclized derivative) was observed so far; a chelating effect of the OH toward the Rh catalyst could be the explanation: the homoallyl alcohol accommodates the large Rh atom, promoting the Markownikoff-type hydrometalation. When the reaction was repeated in the presence of EtOH or NaOAc/AcOH,

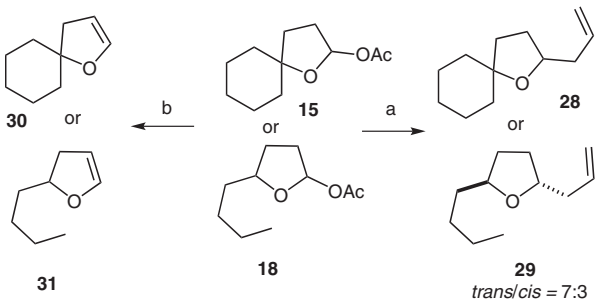
Table 2 Tandem Hydroformylation/Cyclization of Unsaturated Alcohols **8**–**13**

Entry	Alcohol	Reaction conditions[a]	Products	Yield (%)
1	 **8**	MW, THF–H_2O, 110 °C, 60 min, **A** MW, THF NaOAc/AcOH, 110 °C, 30 + 45 min, **A** MW, EtOH, 90 °C, 60 min, **A**	 R = H: **14**, R = Ac: **15**, R = Et: **16**	**14** (67) **15** (70) **16** (77)
2	 **9**	MW, THF–H_2O, 110 °C, 60 min, **A** MW, THF, NaOAc/AcOH, 110 °C, 30 + 45 min, **A** MW, EtOH, 90 °C, 60 min, **A**	 R = H: **17**, R = Ac: **18**, R = Et: **19**	**17** (76) **18** (72) **19** (79)
3	 **10**	MW, THF–H_2O, 110 °C, 60 min, **A** MW, THF, NaOAc/AcOH, 110 °C, 60 min, **A** MW, EtOH, 90 °C, 60 min, **A**	 R = H: **20**, R = Ac: **21**, R = Et: **22**	**20** (60) **21** (70) **22** (70)
4	 **11**	MW, THF–H_2O, 130 °C, 40 min, **A** MW, THF, NaOAc/AcOH, 110 °C, 30 + 45 min, **A**	 R = H: **23a**, R = Ac: **24a**  R = H: **23b**, R = Ac: **24b**	**23a** (62) **24a** (70) **23b** (9) **24b** (11)
5	 **12**	MW, THF–H_2O, 110 °C, 60 min, **A** MW, THF, NaOAc/AcOH, 110 °C, 30 + 45 min, **A**	 R = H: **25** R = Ac: **26**	**25** (72) **26** (89)
6	 **13**	MW, THF, NaOAc/AcOH, 110 °C, 30 + 45 min, **A**	 **27**	**27** (67)
7	**8**	autoclave, THF–H_2O, 110 °C, 12 h, **A** autoclave, THF, NaOAc/AcOH, 110 °C, **A** autoclave, EtOH, 80 °C, 4 h, **A**		**14** (37) **15** (0) **16** (50)
8	**9**	autoclave, THF–H_2O, 110 °C, 12 h, **A** autoclave, THF–H_2O, 60 °C, 24 h, **E** autoclave, THF, NaOAc/AcOH, 80 °C, **A** autoclave, EtOH, 80 °C, 4 h, **A**		**17** (35) **17** (55) **18** (0) **19** (60)
9	**10**	autoclave, THF–H_2O, 110 °C, 12 h, **A** autoclave, EtOH, 80 °C, 4 h, **A**		**20** (0) **22** (70)

[a] **A**: $(PPh_3)_3Rh(CO)H$ (0.01 equiv)/xantphos (0.04 equiv), H_2/CO 827 kPa; **E**: $Rh(CO)_2acac$ (0.01 equiv)/biphephos (0.04 equiv), H_2/CO 1241 kPa.

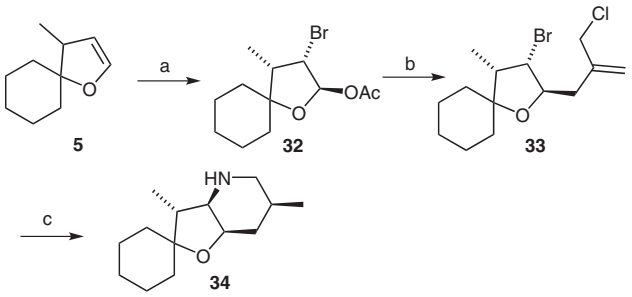
the corresponding derivatives were formed in good yields. For example, reaction on chiral alcohol **13** in the presence of NaOAc/AcOH gave acetoxytetrahydrofuran **27** (Table 2, entry 6), a key intermediate for a concise synthesis of (+)-muscarine.[16] When the alcohols **8**–**10** were submitted to hydroformylation in autoclave under conventional heating (external oil bath), the observed results were highly substrate dependent (Table 2, entries 7–9). Alcohol **8** cyclized towards the same products observed under MW heating, although after longer time and in lower yields. Alcohol **9** gave a mixture of the cyclic and open chain products, while aromatic alcohol **10** formed the expected heterocycles in poor yields. However, working at lower temperature and for longer periods increased the yields and the purity of the products formed in autoclave. When the alcohols **8**–**10** were submitted to hydroformylation in the presence of NaOAc and AcOH under conventional heating, the corresponding 2-acetoxy derivatives **15**, **18**, and **21** were never isolated. However, in the presence of EtOH, 2-ethoxy derivatives **16**, **19**, and **22** were obtained in acceptable yields. The exclusive possibility to introduce an acetoxy group directly at C-2 increased the synthetic potential of the corresponding adducts. Indeed these products can be easy functionalized as demonstrated by the stereoselective reaction of **15** or **18** with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$

(Scheme 4). Compounds **28** or **29** were obtained in good yields (>90% overall from the corresponding allyl alcohols **8** and **9**). Moreover, Et_3N-mediated elimination of acetic acid from **15** and **18** assisted by MWs, afforded dihydrofurans **30** and **31**, versatile intermediates suitable for different transformations.



Scheme 4 *Reagents and conditions*: (a) CH_2=$CHCH_2TMS$, CH_2Cl_2, $BF_3{\cdot}OEt_2$, –78 °C, **28** (95%); **29** (95%); (b) Et_3N, THF, MW, 60 °C, 10 min, **30** (65%); **31** (71%).

As a model reaction for the preparation of the heterocyclic part of cyclopamine, spirodihydrofuran **5** was treated with NBS in water–THF followed by acetylation of the lactol with Ac_2O in pyridine to give compound **32** as a single diastereomer (Scheme 5). Further reaction[17] with 2-(chloromethyl)allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ gave compound **33** in good yield and high stereoselectivity, featuring that the reaction passed through an oxocarbenium ion. Careful NOE experiments suggested that the relative stereochemistries of the substituents around the tetrahydrofuran were 2,3-*trans* and 3,4-*cis*. Then, the secondary bromide and the primary chloride in **33** were substituted with benzylamine under MW heating, producing a piperidine by ring closure. Further treatment with H_2 in the presence of $Pd(OH)_2$/C gave the furanopiperidine **34** in good yields, as a mixture of diastereomers in 8:1 ratio.



Scheme 5 *Reagents and conditions*: (a) NBS, H_2O–THF (1:1), r.t., Ac_2O, pyridine, r.t., 59%; (b) $ClCH_2(C{=}CH_2)CH_2TMS$, $BF_3{\cdot}OEt_2$, $CHCl_3$, –60 °C, 98%; (c) $BnNH_2$, Cs_2CO_3, MeOH, MW, 2 × 3 min, H_2, $Pd(OH)_2$/C, EtOAc, r.t., 52%.

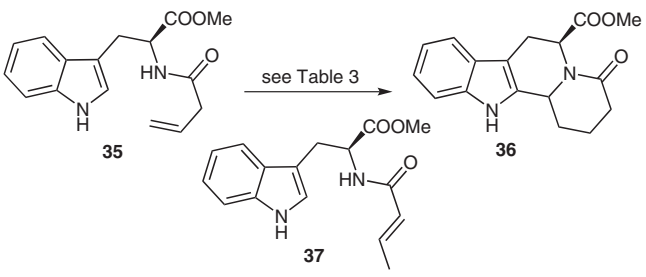
Unfortunately, if compared with cyclopamine,[18] 3′,6′-dimethylhexahydro-3′*H*-spiro(cyclohexane-1,2′-furo[3,2-*b*]pyridine) (**34**) has the wrong stereochemistry at C3a′, as a result of an inversion of configuration that occurs during the nucleophilic substitution of the secondary bromide. However, the above procedure based on a domino hydroformylation/cyclization of an ally alcohol allowed a general and rather short access to new bicyclic furopyridine scaffolds.

Nitrogen (and Carbon) Nucleophiles

The hydroformylation of an alkene in combination with a nitrogen nucleophile has been largely explored for the synthesis of aza-heterocycles.[19] The structures of the products depend on the nature of nucleophiles present in the olefinic substrate. With primary amines, imines are formed, whereas the presence of secondary amines leads to iminium ions (or enamines). With a secondary amide, the lower electron density of the nitrogen affords a more electrophilic acyliminium ion. If a carbon nucleophile is present in the substrate, an additional reaction takes place in a domino multicomponent process. The reactivity of the second C-nucleophile is decisive for the outcome of the domino sequence: with aromatic nucleophiles, the cyclization is often followed by rearomatization; with a π-nucleophile (as an allysilane) the ring closure generates a carbocation that evolves by elimination.[20]

Electron-rich aromatics are excellent partners for Pictet–Spengler cyclizations on acyliminium ions generated by hydroformylation.[21] As the Pictet–Spengler reaction has been reported to occur under MW dielectric heating,[22] we started to explore this process looking at the transformation recently described under conventional heating.[23] Under comparable conditions (Table 3, entry 1), amide **35** was recovered after two hours of MW dielectric heating. The temperature was increased up to 110 °C (changing the ligand to xantphos), but decomposition was observed. Changes in the temperature, solvent, time, and amount of ligands did not result in the expected cyclization product **36** (Table 3, entries 2–7), but only the isomerized product **37** was isolated (Scheme 6). However, conventional heating of **35** with PTSA in an autoclave at 80 °C produced 65% of **36** (Table 3, entry 9).

To better understand the level at which the domino process is hampered, an intermolecular version of the reaction was attempted. Thus, a mixture of the tryptophan methyl ester **38** and oct-1-ene **39** were mixed together and submitted to hydroformylation under different reaction conditions. After 30 minutes of MW dielectric heating in THF, imine **40** was isolated in 56% yields (Scheme 7).



Scheme 6

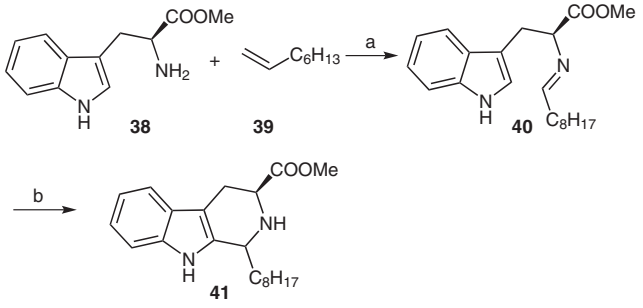
Table 3 Domino Hydroformylation Pictet–Spengler Cyclization

Entry	Reaction conditions[a]	Products (yield, %)
1	MW, THF, 80 °C, PTSA (1 equiv), 2 h, **A**	starting material
2	MW, THF, 110 °C, PTSA (1 equiv), 1 h, **B**	dec.
3	MW, toluene, [bmim][BF_4], PTSA (0.1 equiv), 110 °C, 2 h, **B**	dec.
4	MW, EtOH, PTSA, 110 °C, 30 min, **B**	dec.
5	MW, THF, 70 °C, 5 h, **A**	starting material + **37** (20)
6	MW, THF, 70 °C, PTSA (1 equiv), 5 h, **A**	dec.
7	MW, THF, 70 °C, TFA, (0.5 equiv), 5 h, **A**	dec.
8	MW, THF, 70 °C, 5 h, **C**	**37** (20)
9	autoclave, THF, 80 °C, PTSA (1 equiv), 12 h, **A**	**36** (65)

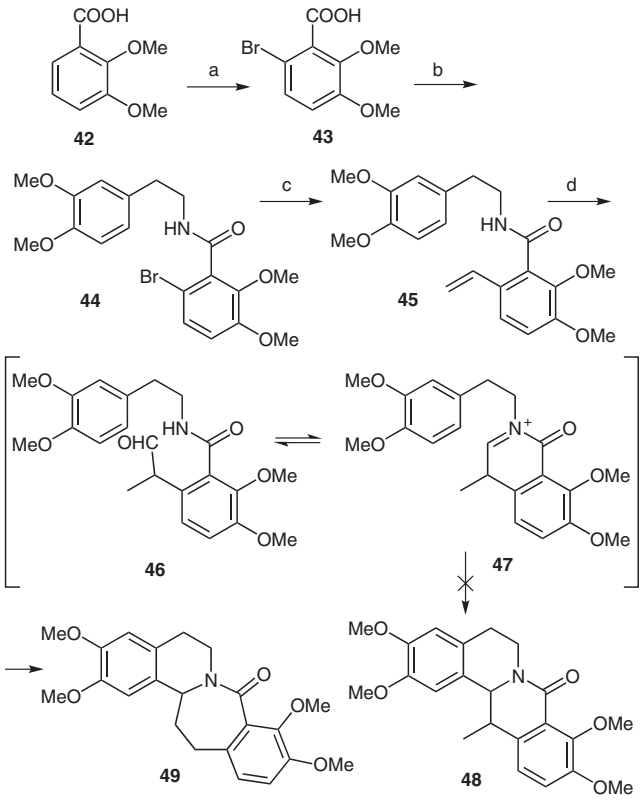
[a] **A**: $Rh(CO)_2$acac (0.01 equiv)/biphephos 0.04 equiv), H_2/CO 827 kPa; **B**: $(PPh_3)_3Rh(CO)H$ (0.01 equiv)/xantphos (0.04 equiv), H_2/CO 827 kPa; **C**: $Rh(CO)_2$acac (0.02 equiv)/biphephos (0.08 equiv), H_2/CO 827 kPa.

Attempts to cyclize **40** under MW irradiation in the presence of different acid additives were unsuccessful. On the other hand, refluxing **40** in toluene for 12 hours in the presence of PTSA gave the cyclization product **41** in 50% yield. This result suggests that the domino process depends on the success of the second reaction. Although there are several reports describing that MW accelerates the Pictet–Spengler reaction, conditions compatible with the MW-assisted hydroformylation process were not found. The influence of the Pictet–Spengler reaction is revealed in the preparation of the 13-methylprotoberberine (**48**) (Scheme 8).[24]

The strategy was based on the hydroformylation (in autoclave) of a suitably decorated styryl **45**, designed to give a branched aldehyde **46** further amenable to the acyliminium ion **47**, the substrate for the Pictet–Spengler cyclization (Scheme 8). Commercially available 2,3-dimethoxybenzoic acid (**42**) was converted by bromination to the bromo acid **43**, then a Schotten–Baumann condensation with homoveratrylamine afforded the amide **44**. The vinyl function was introduced by a Stille coupling under optimized conditions and the vinyl adduct **45** (77%) was obtained, ready for the hydroformylation reaction. At this stage, it has to be emphasized that for styrene like compounds the hydroformylation delivers mainly the branched aldehyde. However, when the reaction was carried out in autoclave [$Rh(CO)_2$acac, biphephos, THF, 80 °C, 12 h, $BF_3{\cdot}OEt_2$], the azepine derivative **49** was obtained in 45% yield.

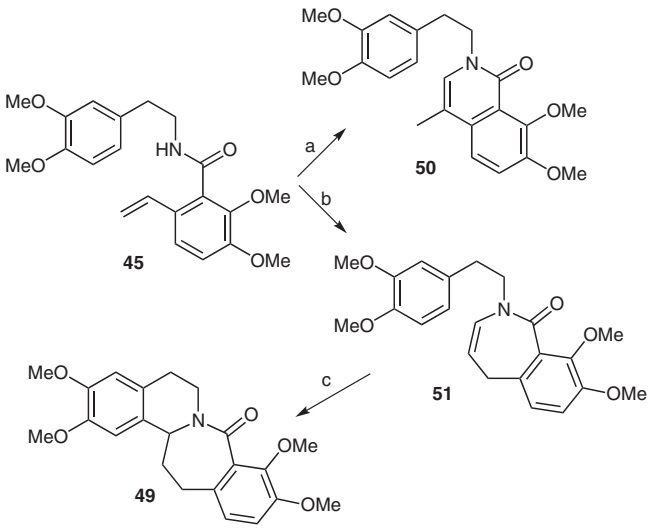


Scheme 7 *Reagents and conditions*: (a) $PPh_3)_3Rh(CO)H$ (0.01 equiv)/xantphos (0.04 equiv), H_2/CO 827 kPa, THF, MW, 110 °C, 1 h, 56%; (b) toluene, reflux, PTSA (1 equiv), 12 h, 50%.



Scheme 8 *Reagents and conditions*: (a) dimethyldibromohydantoin, 0.1 M aq NaOH, 12 h, r.t., 95%; (b) $SOCl_2$, CH_2Cl_2, followed by homoveratrylamine, Et_3N, CH_2Cl_2, r.t., 84%; (c) $Pd(PPh_3)_4$ (0.04 equiv), CH_2=$CHSnBu_3$ (3 equiv), toluene, 100 °C, 12 h, then $Pd(PPh_3)_4$ (0.02 equiv), 24 h, 100 °C, 90%; (d) $Rh(CO)_2$acac (0.01 equiv), biphephos (0.02 equiv), H_2/CO (700 kPa, 1:1), THF, 80 °C, $BF_3{\cdot}OEt_2$ (2 equiv), 12 h, 45%.

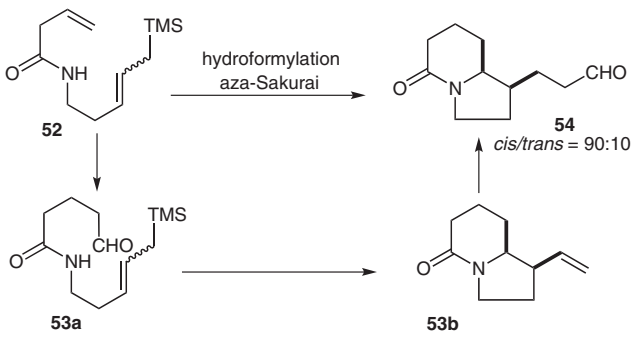
Optimization of the reaction conditions revealed the simultaneous formation of compound **50** and **51**, the latter originated from abnormal linear hydroformylation of the styryl type double bond. Interestingly, the compound **50** coming from the branched aldehyde was by far the major adduct. However, when submitted separately to Pictet–Spengler cyclization, the amide **50** did not cyclize, whereas azepinone **51** gave product **49** in good yield (Scheme 9).



Scheme 9 *Reagents and conditions*: (a) $Rh(CO)_2acac$ (0.01 equiv), Ph_3P (0.02 equiv), H_2/CO (2000 kPa, 1:1), THF, PTSA, 65 °C, 12 h, 76%; (b) $Rh(CO)_2acac$ (0.01 equiv), biphephos (0.02 equiv), H_2/CO (700 kPa, 1:1), THF, PTSA, 85 °C, 24 h, 56%; (c) CH_2Cl_2, reflux $BF_3{\cdot}OEt_2$, 76%.

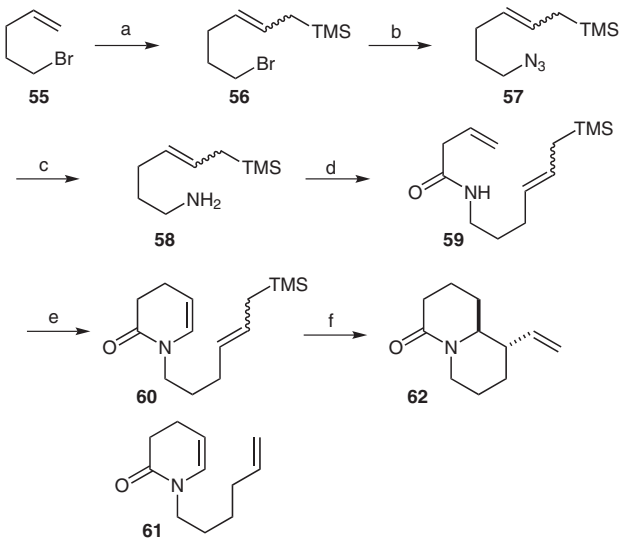
Probably the formation of the acyliminium ion **47** is disfavored with respect to **50** because of a strong conjugation with the aromatic ring. Thus, the fate of the Pictet–Spengler reaction influences the overall domino process proceeding exclusively towards the (unexpected) homoberberine **49**.[25]

The allylsilane is another potential nucleophile that can react with an (acyl)iminium ion. Recently our group reported a domino hydroformylation aza-Sakurai cyclization with the formation of indolizidine **54** (Scheme 10).[26]



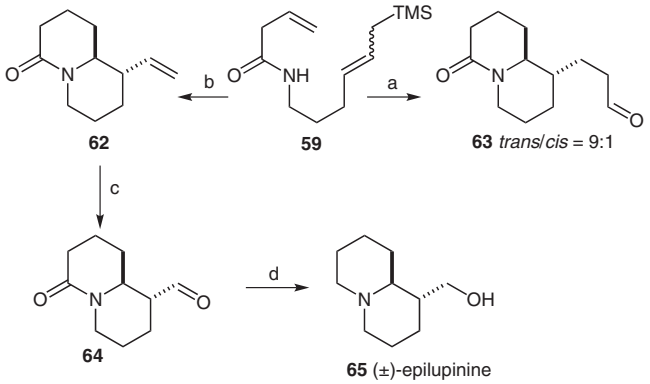
Scheme 10 Domino hydroformylation by aza-Sakurai cyclization

In this case, the intermediate aldehyde **53a** cyclized to the bicyclic alkene **53b**, a substrate for a further hydroformylation towards linear aldehyde **54**. With the idea of synthesizing the quinolizidine alkaloid (±)-epilupinine, the allylsilane **59** was prepared as described in Scheme 11. Starting from 5-bromopent-1-ene (**55**), the allylsilane part was introduced by a metathetic process giving the bromo allylsilane **56**. Then, bromide displacement by sodium azide followed by $LiAlH_4$ reduction delivered the amine **58**. Finally coupling with vinylacetic acid yielded the amidoallylsilane **59**. Hydroformylation of **59** was carried out under MW dielectric heating under different conditions. As in the previous case, the expected overall domino process did not go to completion and enamine **60** was the main product isolated together with about 20% of **61** coming from protodesilylation. Attempts to optimize the reaction were not successful. However, allylsilane **60** cyclized in the presence of TFA to give the quinolizidine **62**. Conversely, when submitted to cyclizative hydroformylation in an autoclave in the presence of an acid additive, allylsilane **59** afforded the quinolizinyl aldehyde **63** with good diastereoselectivity.



Scheme 11 *Reagents and conditions*: (a) $CH_2{=}CHCH_2SiMe_3$ (4 equiv), Grubbs II (0.01 equiv), CH_2Cl_2, reflux, 12 h, 81%; (b) NaN_3 (3 equiv), DMF, 70 °C, 12 h, 78%; (c) $LiAlH_4$ (2 equiv), THF, 3 h, r.t., 90%; (d) vinylacetic acid (1 equiv), EDC·HCl (1 equiv), HOBt (0.2 equiv), CH_2Cl_2, 12 h, 93%; (e) $Rh(CO)_2acac$ (0.02 equiv), biphephos (0.08 equiv), CO/H_2 827 kPa, PPTS (0.1 equiv), THF, MW, 60 °C, 2 h, 49%; (f) TFA, r.t., 12 h, 62%.

If the same reaction was performed sequentially omitting the Lewis acid during the hydroformylation step, the final linear hydroformylation did not proceed; instead quinolizidine **62** was isolated in good yield. A direct application of this sequence to the synthesis of epilupinine progressed with the ozonolysis of the *exo* double bound to give the aldehyde **64**, which was reduced to (±)-epilupinine, obtained in 22% overall yield over seven steps from bromopentene **55** (Scheme 12).



Scheme 12 *Reagents and conditions*: (a) $Rh(CO)_2(acac)$ (0.01 equiv), biphephos (0.02 equiv), CSA (1 equiv), MS 4Å, 500 kPa H_2/CO (1:1), MeCN, 70 °C, 10 h, 78%; (b) $Rh(CO)_2(acac)$ (0.01 equiv), biphephos (0.03 equiv), MS 4 Å, 500 kPa H_2/CO (1:1), MeCN, 65 °C, 65%; (c) O_3, CH_2Cl_2, –78 °C to r.t., then, Ph_3P (1 equiv) 76%; (d) $LiAlH_4$ (5 equiv), THF, 5 h, r.t., 70%.

Although useful to simplify and speed up the traditionally time consuming process of hydroformylation, MW-assisted domino hydroformylation processes are limited by the sensitivity to the nucleophiles. With allyl alcohols MW gave results superior to the standard autoclave process, allowing a rapid access to lactols or 2-acetoxytetrahydrofurans. The reaction was reproducible and also the formation of classical by-products was minimized. On the other hand, MW dielectric heating seems not compatible for instance with the reactivity of acyliminium ions: a partial degradative pathway is operating owing to the hot spots generated by microwave irradiation. From our present experience, both devices MW irradiation and autoclave heating are complementary for performing hydroformylations. But it remains that the MW process has to be tried at first, as it gives faster reaction rate and in case of failure the traditional autoclave can be a valuable resort. Finally regardless of the apparatus, hydroformylation is a powerful reaction not only for introducing an aldehyde function but even better if the olefin substrate is properly designed, it becomes a powerful tool for performing domino reactions. A few of them have been presented here; we believe that they will stimulate the organic chemists to add many more examples in near future.

The reactions were carried out in oven dried or flamed vessels and performed under argon. Solvents were dried and purified by conventional methods prior use. Petroleum ether (PE) used refers to the fraction boiling in the range 40–60 °C. Flash column chromatography was performed with Merck silica gel 60, 0.040–0.063 mm (230–400 mesh). Merck aluminum backed plates precoated with silica gel 60 (UV_{254}) were used for TLC and were visualized by staining with $KMnO_4$. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 400 MHz instrument at 400 and at 200 MHz, respectively. Low-resolution mass spectra were obtained on an Agilent 1100 LC/MS instrument in positive or negative mode. GC/MS analysis was performed on a Varian-GC using a CP 8944 column (30 m × 0.250 mm × 0.39 μm. For MW reaction a CEM Discover microwave oven equipped with an 80 or 10 mL tube for reactions under pressure (CEM Corporation) was employed. A 50 ML stainless lab autoclave was employed for other processes.

4-Methyl-1-oxaspiro[4.5]decan-2-ol (3); Typical Procedure

In an 80 mL microwave tube $(PPh_3)_3Rh(CO)H$ (131 mg, 0.14 mmol) and xantphos (330 mg, 0.57 mmol) were added to a solution of compound **1** (1.00 g, 7.14 mmol) in a mixture of THF–H_2O (10:1, 10 mL). The solution was pressurized with syngas at 827 kPa and heated to 110 °C (3 × 30 min) by microwave irradiation at 150 W. The flask was cooled and the internal gas released. The residue was dried (Na_2SO_4), and after filtration and evaporation, the crude was purified by flash chromatography (PE–EtOAc, 6:1) to give **3** (1.12 g, 90%) as a yellow oil consisting of a mixture of two diastereomers; diastereomeric ratio: 60:40.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.47–5.40 (m, 1 H), 3.02 (d, *J* = 23.0 Hz, 1 H), 2.39–2.31 (m, 1 H), 2.28–2.10 (m, 1 H), 2.03–1.98 (m, 1 H), 1.75–1.10 (m, 10 H), 0.98–0.88 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 97.7, 88.20, 39.5, 38.8, 37.1, 31.3, 25.6, 22.9, 16.0.

ESI-MS: *m*/*z* (%) = 193 (100, $[M + Na]^+$), 171 (35, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{18}O_2$ + Na: 193.2385; found: 193.2380.

2-Ethoxy-4-methyl-1-oxaspiro[4.5]decane (4); Typical Procedure

In a 10 mL microwave vessel $(PPh_3)_3Rh(CO)H$ (104 mg, 0.11 mmol) and xantphos (264 mg, 0.45 mmol) were added to a solution of compound **1** (800 mg, 5.71 mmol) in EtOH (2 mL). The solution was pressurized with syngas at 827 kPa and heated to 110 °C (3 × 30 min) by microwave irradiation at 150 W. The flask was cooled and the internal gas released. The residue was dried (Na_2SO_4) and after filtration and evaporation, the crude was purified by flash chromatography (PE–EtOAc, 8:1) to give **4** (748 mg, 67%) as a yellow oil consisting of a mixture of two diastereomers; diastereomeric ratio: 60:40.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.09–4.97 (m, 1 H), 3.88–3.67 (m, 1 H), 3.52–3.31 (m, 1 H), 2.43–2.32 (m, 1 H), 2.31–1.92 (m, 1 H), 1.83–1.33 (m, 10 H), 1.29–1.02 (m, 3 H), 1.01–0.88 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.4, 87.91, 60.0, 40.7, 38.8, 37.1, 32.1, 25.9, 22.9, 16.04, 15.2.

ESI-MS: *m*/*z* (%) = 221 (100, $[M + Na]^+$), 198 (26, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{22}O_2$ + Na: 221.2916; found: 221.2910.

4-Methyl-1-oxaspiro[4.5]dec-2-yl Acetate (6); Typical Procedure

In a 10 mL microwave tube a solution of $(PPh_3)_3Rh(CO)H$ (14 mg, 0.015 mmol) and xantphos (35 mg, 0.060 mmol) in THF–H_2O (10:1, 2 mL) was added to a solution of **1** (100 μL, 0.75 mmol), AcOH (43 μL, 0.75 mmol) and NaOAc (61 mg, 0.75 mmol) in THF–H_2O (10:1, 2 mL) under an inert atmosphere. The solution was submitted to pressurized syngas at 827 kPa and heated for 60 min at 110 °C by microwave irradiation at 150 W (value previously settled on the microwave oven). The flask was cooled and the internal gas released. Sat. aq Na_2CO_3 (4 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4). After filtration and concentration in vacuo, the crude mixture was purified by flash chromatography (PE–EtOAc, 6:1) to give **6** as a pale yellow oil (109 mg, 88%) consisting of a mixture of two diastereomers; diastereomeric ratio: 60:40.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.03 (s-like, 1 H), 2.24 (m, 3 H), 2.10 (s, 3 H), 1.70–1.40 (m, 12 H), 1.04 (d, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 96.0, 89.1, 38.9, 37.9, 37.5, 31.1, 22.9, 21.2, 16.0.

ESI-MS: *m*/*z* (%) = 235 (100, $[M + Na]^+$), 213 (50, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{20}O_3$ + Na: 235.2752; found: 235.2751.

1-Oxaspiro[4.5]decan-2-ol (14)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.41 (s-like, 1 H), 3.85 (br s, 1 H), 2.11–1.90 (m, 4 H), 1.58–1.40 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 100.7, 89.9, 38.7, 35.5, 34.4, 32.2, 25.8, 23.7.

ESI-MS: *m*/*z* (%) = 179 (100, $[M + Na]^+$), 157 (26, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_9H_{16}O_2$ + Na: 179.2119; found: 179.2120.

1-Oxaspiro[4.5]dec-2-yl Acetate (15)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.96 (s-like, 1 H), 2.15–1.50 (m, 14 H), 2.10 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 97.6, 87.7, 38.6, 35.5, 34.2, 30.8, 23.7, 21.2.

ESI-MS: *m*/*z* (%) = 221 (100, $[M + Na]^+$), 199 (48, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{18}O_3$ + Na: 221.2486; found: 221.2482.

2-Ethoxy-1-oxaspiro[4.5]decane (16)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.07 (s-like, 1 H), 3.67–3.53 (m, 2 H), 2.14–1.90 (m, 4 H), 1.58–1.40 (m, 10 H), 1.18 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 100.3, 86.7, 62.0, 39.5, 36.3, 34.9, 30.4, 25.8, 23.8, 15.8.

ESI-MS: *m*/*z* (%) = 207 (100, $[M + Na]^+$), 185 (70, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{20}O_2$ + Na: 207.2651; found: 207.2645.

5-Butyltetrahydrofuran-2-ol (17)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.43 (s-like, 1 H), 4.07–3.99 (m, 2 H), 1.89 (m, 2 H), 1.65 (m, 3 H), 1.40 (m, 5 H), 0.90 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 99.8, 79.9, 33.1, 32.8, 31.6, 27.9, 22.8, 14.6.

ESI-MS: *m*/*z* (%) = 167 (100, $[M + Na]^+$), 144 (40, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_8H_{16}O_2$ + Na: 167.2012; found: 167.2009.

5-Butyltetrahydrofuran-2-yl Acetate (18)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.89 (s-like, 1 H), 4.14 (m, 1 H), 1.95 (s, 3 H), 1.85–1.40 (m, 10 H), 0.88 (s-like, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 98.2, 1 80.3, 33.4, 32.9, 31.7, 27.3, 22.7, 21.2, 14.2.

ESI-MS: *m*/*z* (%) = 209 (100, $[M + Na]^+$), 187 (56, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{18}O_3$ + Na: 209.2379; found: 209.2375.

2-Butyl-5-ethoxytetrahydrofuran (19)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.91 (s-like, 1 H), 4.00 (m, 1 H), 3.67 and 3.55 (m, 2 H), 1.75–1.62 (m, 4 H), 1.40 (m, 4 H), 1.18 (t, *J* = 6 Hz, 3 H), 0.86 (s-like, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 105.2, 80.8, 61.8, 33.9, 33.0, 31.9, 23.3, 22.3, 14.3, 14.0.

ESI-MS: *m*/*z* (%) = 195 (100, $[M + Na]^+$), 173 (30, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{20}O_2$ + Na: 195.2544; found: 195.2540.

5-Phenyltetrahydrofuran-2-ol (20)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 5.57 (s-like, 1 H), 5.14 (s-like, 1 H), 3.93 (br s, 1 H), 2.24–1.96 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 127.8, 127.9, 127.0, 100.3, 80.2, 33.6, 31.0.

ESI-MS: *m*/*z* (%) = 187 (100, $[M + Na]^+$), 165 (50, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{12}O_2$ + Na: 187.1908; found: 187.1901.

5-Phenyltetrahydrofuran-2-yl Acetate (21)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 5 H), 5.21 (s-like, 1 H), 5.04 (s-like, 1 H), 2.27–1.90 (m, 4 H), 1.95 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 141.8, 128.2, 128.9, 127.0, 98.9, 80.2, 34.4, 31.1, 21.1.

ESI-MS: *m*/*z* (%) = 229 (100, $[M + Na]^+$), 207 (60, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{14}O_3$ + Na: 229.2275; found: 229.2270.

2-Ethoxy-5-phenyltetrahydrofuran (22)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 5 H), 5.10 (s-like, 2 H), 3.67 and 3.53 (m, 2 H), 2.26–1.90 (m, 4 H) 1.18 (t, *J* = 6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.6, 128.1, 128.0, 127.3, 105.6, 81.7, 61.8, 33.9, 31.4, 15.7.

ESI-MS: *m*/*z* (%) = 215 (100, $[M + Na]^+$), 193 (50, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{16}O_2$ + Na: 214.2440; found: 2145.24436.

6-Phenyltetrahydro-2*H*-pyran-2-yl Acetate (24a)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 5 H), 5.69 (s-like, 1 H), 4.79 (dd, *J* = 8, 2 Hz, 1 H), 2.10 (s, 3 H), 1.9–1.36 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 143.6, 128.8, 127.9, 127.4, 94.1, 76.3, 31.5, 29.7, 21.3, 19.9.

ESI-MS: *m*/*z* (%) = 243 (100, $[M + Na]^+$), 221 (56, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{16}O_3$ + Na: 243.2541; found: 243.2540.

4-Methyl-5-phenyltetrahydrofuran-2-yl Acetate (24b)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 2 H), 7.27 (m, 1 H), 7.02 (m, 2 H), 6.04 (s-like, 1 H), 4.70 (d, *J* = 8 Hz, 1 H), 2.58 (m, 1 H), 2.28 (m, 1 H), 2.10 (s, 3 H), 1.66 (m, 1 H), 1.06 (d, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 137.7, 18.5, 128.0, 127.1, 97.3, 86.1, 40.4, 37.0, 21.3, 16.5.

ESI-MS: *m*/*z* (%) = 243 (100, $[M + Na]^+$), 221 (13, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{16}O_3$ + Na: 243.2541; found: 243.2538.

4-Methyltetrahydrofuran-2-ol (25)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.36 (s-like, 1 H), 3.90 (m, 2 H), 3.52 (m, 1 H), 2.62 (m, 1 H), 1.73 (m, 1 H), 1.39 (m, 1 H), 0.96 (d, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 99.0, 74.7, 42.4, 31.9, 16.1.

ESI-MS: *m*/*z* (%) = 125 (100, $[M + Na]^+$), 103 (25, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_5H_{10}O_2$ + Na: 125.1215; found: 125.1212.

4-Methyltetrahydrofuran-2-yl Acetate (26)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 (s-like, 1 H), 3.95 (m, 1 H), 3.59 (m, 1 H), 2.68 (m, 1 H), 2.10 (m, 1 H), 2.08 (s, 3 H), 1.49 (m, 1 H), 0.98 (d, *J* = 8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 96.5, 78.3, 40.9, 31.2, 21.1, 16.1.

ESI-MS: *m*/*z* (%) = 167 (100, $[M + Na]^+$), 145 (20, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_7H_{12}O_3$ + Na: 167.1581; found: 167.1578.

5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)tetrahydrofuran-2-yl Acetate (27)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.97 (s-like, 1 H), 4.09 (m, 1 H), 3.55 (m, 2 H), 1.92–1.75 (m, 4 H), 1.91 (s, 3 H), 0.91 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 97.2, 82.6, 62.1, 33.0, 25.3, 25.1, 21.1, 18.3, –5.4.

ESI-MS: *m*/*z* (%) = 275 (100, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{27}O_4Si$: 275.4366; found: 275.4362.

2-Allyl-1-oxaspiro[4.5]decane (28); Typical Procedure

To a solution of **15** (100 μL, 0.75 mmol) in EtOH-free $CHCl_3$ (10 mL) was added $BF_3{\cdot}OEt_2$ (120 μL, 0.97 mmol) at –60 °C and the reaction mixture was stirred for 15 min. Allyltrimethylsilane (87 μL, 0.75 mmol) was added dropwise and the mixture was stirred at r.t. for 12 h. The residue was treated with aq $NaHCO_3$ (5 mL) and extracted with Et_2O (2 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to afford 135 mg (95%) of **28**, which was not purified further.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81–5.74 (m, 1 H), 5.05–4.97 (m, 2 H), 3.96–3.93 (m, 1 H), 2.34–2.29 (m, 1 H), 2.19–2.14 (m, 1 H), 1.91–1.88 (m, 1 H), 1.69–1.28 (m, 15 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.2, 116.4, 79.7, 78.3, 38.6, 37.6, 37.1, 36.1, 30.9, 23.1.

ESI-MS: *m*/z (%) = 203 (100, $[M + Na]^+$), 181 (45, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{20}O$ + Na: 203.2764; found: 203.2760.

2-Allyl-5-butyltetrahydrofuran (29)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87–5.80 (m, 1 H), 5.11–5.06 (m, 2 H), 4.00 (m, 1 H), 3.91 (m, 1 H), 2.34–2.29 (m, 2 H), 1.83 (m, 1 H), 1.60 (m, 6 H), 1.40 (m, 2 H), 0.93 (t, *J* = 6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.9, 116.1, 80.6, 79.8, 38.5, 36.4, 33.9, 33.0, 27.4, 22.4, 14.1.

ESI-MS: *m*/*z* (%) = 191 (100, $[M + Na]^+$), 168 (45, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{20}O$ + Na: 191.2657; found: 191.2651.

1-Oxaspiro[4.5]dec-2-ene (30); Typical Procedure

A solution of **15** (99 mg, 0.5 mmol) in THF (1 mL) was mixed with Et_3N (100 mg, 1 mmol) inside a microwave vial. The vial was heated to 60 °C under microwave irradiation (max internal pressure 827 kPa, 150 W) for 10 min. The solvent was evaporated and the crude purified by column chromatography (pentane–Et_2O, 10:1); yield: 44 mg (65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.41 (s-like, 1 H), 4.82 (s-like, 1 H), 2.49 (s, 2 H), 1.58–1.43 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.3, 100.2, 81.5, 45.2, 32.1, 25.8, 23.0.

ESI-MS: *m*/*z* (%) = 161 (100, $[M + Na]^+$), 139 (40, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_9H_{14}O$ + Na: 161.1966; found: 161.1963.

2-Butyl-2,3-dihydrofuran (31)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.45 (s-like, 1 H), 4.87 (s-like, 1 H), 4.39 (m, 1 H), 2.50 (s, 1 H), 2.18 (s, 1 H), 1.74 (m, 1 H), 1.37 (m, 4 H), 0.89 (t, *J* = 6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.4, 101.1, 80.3, 41.9, 30.6, 27.9, 22.9, 13.5.

ESI-MS: *m*/*z* (%) = 149 (100, $[M + Na]^+$), 127 (30, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_8H_{14}O$ + Na: 149.1859; found: 149.1854.

3-Bromo-4-methyl-1-oxaspiro[4.5]dec-2-yl Acetate (32)

To a solution of **5** (200 mg, 1.32 mmol) in anhyd THF (5 mL) were added *N*-bromosuccinimmide (258 mg, 1.45 mmol) and H_2O (0.5 mL) portionwise and the reaction mixture stirred at r.t. for 10 min. The residue was dried (Na_2SO_4) and after filtration and evaporation, the crude was dissolved in $CHCl_3$ (5 mL). Ac_2O (37 μL, 0.39 mmol) and pyridine (114 μL, 1.41 mmol) were added under N_2. The mixture was stirred at r.t. for 12 h. The residue was treated with aq $NaHCO_3$ (5 mL) and extracted with $CHCl_3$ (3 × 10 mL) and the combined organic layers were dried (Na_2SO_4). After filtration and evaporation, the crude was purified by flash chromatography (PE–Et_2O, 2:1) to give **32** (41 mg, 59%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.35 (s, 1 H), 4.34 (d, *J* = 5.6 Hz, 1 H), 2.29–2.26 (m, 1 H), 2.29–2.25 (m, 2 H), 2.00 (s, 3 H), 1.64–1.45 (m, 8 H), 1.10 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 100.4, 89.8, 53.2, 47.6, 39.1, 32.1, 25.4, 22.1, 20.1, 12.4

ESI-MS: *m*/*z* (%) = 315/312 (100, $[M + Na]^+$), 292/290 $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{19}BrO_3$ + Na: 314.1712; found: 314.1708.

3-Bromo-2-[2-(chloromethyl)prop-2-en-1-yl]-4-methyl-1-oxaspiro[4.5]decane (33)

To a solution of **32** (90 mg, 0.30 mmol) in EtOH-free $CHCl_3$ (10 mL) was added $BF_3{\cdot}OEt_2$ (59 μL, 0.46 mmol) at –60 °C and the reaction mixture was stirred for 15 min. 2-(Chloromethyl)allyltrimethylsilane (83 μL, 0.46 mmol) was added dropwise and the mixture was stirred at r.t. for 12 h. The residue was treated with aq $NaHCO_3$ (5 mL) and extracted with Et_2O (2 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give **33** (96 mg, 98%), which was used in the next reaction without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.23 (s, 1 H), 5.10 (s, 1 H), 4.29–4.24 (m, 1 H), 4.22–4.19 (m, 1 H), 4.14 (d, *J* = 10.4 Hz, 2 H), 2.53 (dd, *J* = 4.4, 12.1 Hz, 1 H), 2.38 (dd, *J* = 7.2, 20.2 Hz, 1 H), 2.01–1.97 (m, 1 H), 1.65–1.41 (m, 8 H), 1.26–1.14 (m, 2 H), 1.06 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.23, 116.96, 84.38, 83.20, 58.27, 48.62, 45.44, 38.25, 38.00, 30.55, 25.68, 23.10, 22.07, 13.43.

ESI-MS: *m*/*z* (%) = 345/343 (100, $[M + Na]^+$), 323/321 (54, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{22}BrClO$ + Na: 344.6703; found: 344.6700.

3′,6′-Dimethylhexahydro-3′*H*-spiro[cyclohexane-1,2′-furo[3,2-*b*]pyridine] (34)

To a solution of **33** (30 mg, 0.09 mmol) in MeOH (2 mL) in a 10 mL microwave tube was added benzylamine (3 μL, 0.28 mmol) followed by Cs_2CO_3 (32 mg, 0.1 mmol) and the reaction mixture was irradiated 2 times by microwaves at 100 °C for 3 min (power max

150 W). The residue was evaporated and the crude was dissolved in EtOAc (5 mL) and $Pd(OH)_2/C$ (10 mg) was added. The mixture was stirred under H_2 (100 kPa) for 12 h at r.t. After filtration, the solvent was evaporated and the residue was purified by flash chromatography (PE–Et_2O, 1:1) to give **34** (14 mg, 52%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.27 (m, 1 H), 2.98 (m, 1 H), 2.19 (m, 2 H), 1.83–1.23 (m, 14 H), 1.10 (d, *J* = 5 Hz, 3 H), 0.92 (d, *J* = 8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 89.6, 75.4, 65.8, 52.3, 44.2, 39.6, 39.0, 32.0, 31.2, 25.9, 22.5, 18.3, 8.4.

ESI-MS: *m*/*z* (%) = 224 (100, $[M + H]^+$).

ESI-HMRS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{26}NO$: 224.3624; found: 224.3620.

6-Bromo-2,3-dimethoxybenzoic Acid (43)

In an ice bath, 2,3-dimethoxybenzoic acid (**42**; 1 g, 5.49 mmol) and 1,3-dibromo-5,5-dimethylhydantoin (863 mg, 3.02 mmol) were added to 0.7 M aq NaOH (8.6 mL). The reaction mixture was stirred at r.t. for 2 h, then 1 M aq HCl (15 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give **43** as a solid (1.433 g, 98%), which was used without further purification; mp 110–112 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.92 (br s, 1 H), 7.27 (d, *J* = 8.7 Hz, 1 H), 6.85 (d, *J* = 8.7 Hz, 1 H), 3.92 (s, 3 H), 3.87 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 152.2, 147.1, 130.7, 128.2, 114.9, 108.7, 62.0, 56.2.

ESI-HMRS: *m*/*z* $[M + H]^+$ calcd for $C_9H_9BrO_4$: 260.9762; found: 260.9755.

6-Bromo-*N*-(3,4-dimethoxyphenethyl)-2,3-dimethoxybenzamide (44)

$SOCl_2$ (0.80 mL, 10.98 mmol) was added to a solution of **43** (1.433 g, 5.49 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at reflux for 2 h, cooled to r.t. and concentrated. In an ice bath, the residue was dissolved in CH_2Cl_2 (10 mL), then Et_3N (1.53 mL, 10.98 mmol) and 3,4-dimethoxyphenethylamine (1.39 mL, 8.23 mmol) were added. The mixture was stirred at r.t. for 12 h. Then, 1 M aq HCl (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (pentane–EtOAc, 50:50) to give **44** as a yellow solid (1.951 g, 84%); mp 100–102 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.7 Hz, 1 H), 6.81–6.77 (m, 4 H), 5.76 (br t, *J* = 6.0 Hz, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.72 (q, *J* = 6.5 Hz, 2 H), 2.89 (t, *J* = 6.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 152.4, 149.2, 147.8, 147.0, 134.2, 131.4, 128.2, 120.9, 114.3, 112.3, 111.6, 109.8, 62.2, 56.2, 56.1, 56.6, 41.2, 35.4.

ESI-MS: *m*/*z* = 424 $[M + H]^+$.

***N*-(3,4-Dimethoxyphenethyl)-2,3-dimethoxy-6-vinylbenzamide (45)**

Vinyltributylstannane (0.98 mL, 3.35 mmol) and $Pd(PPh_3)_4$ (52 mg, 0.04 mmol) were added to a solution of **44** in toluene (7 mL). The reaction mixture was stirred under argon at 100 °C for 12 h. After cooling, additional $Pd(PPh_3)_4$ (26 mg, 0.02 mmol) was added and the mixture was stirred at 100 °C for 24 h. After cooling and concentration, the residue was purified by flash chromatography (pentane–EtOAc, 50:50) to give **45** (375 mg, 90%); mp 117–119 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.5 Hz, 1 H), 6.87 (d, *J* = 8.5 Hz, 1 H), 6.83–6.73 (m, 3 H), 6.66 (dd, *J* = 17.4, 11.1 Hz, 1 H), 5.90 (br t, *J* = 6.2 Hz, 1 H), 5.57 (dd, *J* = 17.5, 1.0 Hz, 1 H), 5.16 (dd, *J* = 10.9, 1.0 Hz, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.71 (q, *J* = 6.5 Hz, 2 H), 2.86 (t, *J* = 6.9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 152.1, 149.1, 147.7, 145.5, 133.3, 131.5, 131.4, 128.6, 121.5, 120.8, 114.5, 113.2, 112.1, 111.5, 61.8, 56.0, 55.9, 41.0, 35.4.

ESI-MS: *m*/*z* = 372 $[M + H]^+$.

2-(3,4-Dimethoxyphenethyl)-7,8-dimethoxy-4-methylisoquinolin-1(2*H*)-one (50)

In a stainless steel autoclave under an inert atmosphere, a solution of $Rh(CO)_2$acac (1.5 mg, 0.006 mmol) and Ph_3P (7.1 mg, 0.023 mmol) in anhyd degassed THF (3 mL) (prepared in a Schlenk glassware under an inert atmosphere) was added to a solution of **45** (106 mg, 0.285 mmol) and PTSA (5.4 mg, 0.029 mmol) in anhyd degassed THF to reach a final concentration of 0.04 M. The autoclave was flushed three times with H_2/CO (1:1). Then, the autoclave was filled with 2000 kPa of H_2/CO (1:1) and was heated at 65 °C with stirring for 12 h. The autoclave was cooled to r.t. and the gases were slowly and carefully released. After cooling, the reaction mixture was concentrated under reduced pressure to give an oil. The residue was purified by flash chromatography (pentane–EtOAc, 20:80) to give **50** (83 mg, 76%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 2 H), 6.79 (br s, 2 H), 6.74 (s, 1 H), 6.60 (s, 1 H), 4.10 (dd, *J* = 9.4, 7.3 Hz, 2 H), 4.00 (s, 3 H), 3.96 (s, 3 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 3.02 (dd, *J* = 8.4, 6.7 Hz, 2 H), 2.16 (d, *J* = 0.9 Hz, 3 H).

ESI-HMRS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{25}NO_5$: 384.1811; found: 384.1806

2-(3,4-Dimethoxyphenethyl)-8,9-dimethoxy-2,5-dihydro-1*H*-benzo[*c*]azepin-1-one (51)

In a stainless steel autoclave under an inert atmosphere, a solution of $Rh(CO)_2$acac (1.4 mg, 0.005 mmol) and biphephos (8.5 mg, 0.011 mmol) in anhyd degassed THF (3 mL) (prepared in a Schlenk glassware under an inert atmosphere) was added to a solution of **45** (100 mg, 0.269 mmol) and PTSA (5.1 mg, 0.027 mmol) in anhyd degassed THF to reach a final concentration of 0.04 M. The autoclave was flushed three times with H_2/CO (1:1). Then, the autoclave was filled with 700 kPa of H_2/CO (1:1) and was heated at 85 °C with stirring for 12 h. The autoclave was cooled to r.t. and the gases were slowly and carefully released. The reaction mixture was then concentrated under reduced pressure to give an oil. The residue was purified by flash chromatography (pentane–EtOAc, 30:70) to give **51** (58 mg, 56%) as a yellow waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87–6.78 (m, 4 H), 6.72 (d, *J* = 8.1 Hz, 1 H), 5.72 (d, *J* = 7.3 Hz, 1 H), 5.64 (td, *J* = 7.5, 6.6 Hz, 1 H), 4.30 (br s, 1 H), 3.987 (s, 3 H), 3.85 (br s, 9 H), 3.50 (br s, 1 H), 3.19 (br d, *J* = 9.1 Hz, 1 H), 3.04 (br d, *J* = 6.7 Hz, 1 H), 2.91–2.81 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 152.0, 149.2, 149.0, 147.7, 138.1, 131.6, 129.6, 128.9, 121.4, 121.0, 120.7, 114.1, 112.4, 111.4, 62.0, 56.2, 56.0, 56.0, 49.9, 34.3, 30.7.

ESI-HMRS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{25}NO_5$: 384.1811; found: 384.1816.

2,3,9,10-Tetramethoxy-5,6,14,14a-tetrahydrobenzo-[5,6]azepino[2,1-*a*]isoquinolin-8(13*H*)-one (49)

To a solution of compound **51** (58 mg, 0.15 mmol) in anhyd CH_2Cl_2 (4 mL) was added dropwise BF_3·OEt_2 (33 μL, 0.30 mmol) and the reaction mixture was stirred at reflux for 12 h. After cooling, sat. aq Na_2CO_3 (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by

flash chromatography (pentane–EtOAc, 40:60) to give **49** (49 mg, 76%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (d, *J* = 8.2 Hz, 1 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 6.67 (s, 1 H), 6.45 (s, 1 H), 4.50 (dd, *J* = 9.5, 7.9 Hz, 1 H), 4.32 (ddd, *J* = 13.0, 6.3, 5.0 Hz, 1 H), 3.96 (s, 3 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.77 (s, 3 H), 3.61 (ddd, *J* = 13.0, 8.3, 4.6 Hz, 1 H), 2.98–2.77 (m, 3 H), 2.71–2.65 (m, 1 H), 2.13–2.07 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 152.4, 148.0, 147.8, 147.6, 130.4, 129.5, 127.7, 127.0, 123.2, 113.9, 111.5, 109.3, 62.0, 56.1, 56.0, 54.6, 38.1, 37.7, 30.0, 28.6.

ESI-HMRS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{26}NO_4$: 384.4376; found: 384.4372.

6-(Bromohex-2-enyl)trimethylsilane (56)

To a solution of 5-bromopent-1-ene (**55**; 400 mg, 2.68 mmol) and allyltrimethylsilane (2.14 mL, 13.42 mmol) in anhyd degassed CH_2Cl_2 (14 mL) was added 2nd generation Grubbs catalyst (23 mg, 0.027 mmol). The reaction mixture was stirred at reflux for 12 h, cooled to r.t., and concentrated. The residue was purified by flash chromatography (pentane) to give **56** (509 mg, 81%, 70:30 *E*/*Z*) as a colorless liquid; bp 97–99 °C/760 Torr.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.45–5.42 (m, 1 H), 5.31–5.14 (m, 1 H), 3.46–3.39 (m, 2 H), 2.26–2.11 (m, 2 H), 1.99–1.87 (m, 2 H) 1.24–1.30 (m, 2 H), 0.07–0.00 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.2, 126.5, 124.5, 123.3, 33.3, 33.0, 31.9, 31.2, 22.9, 22.8, 18.7, 18.0, –1.8, –1.5.

ESI-HMRS: *m*/*z* [M + H]$^+$ calcd for $C_9H_{19}BrSi$: 235.0518; found: 235.0522.

6-(Azidohex-2-enyl)trimethysilane (57)

To a solution of **56** (187 mg, 0.80 mmol) in anhyd DMF (10 mL) was added NaN_3 (155 mg, 2.39 mmol). The mixture was stirred 5 h at 70 °C, then diluted with H_2O (20 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give **57** as a colorless oil (122 mg, 78%, 70:30 *E*/*Z*), which was used without further purification.

IR (neat): 2954, 2094, 1246, 854 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.62–5.42 (m, 1 H), 5.30–5.18 (m, 1 H), 3.26 (q, *J* = 6.9 Hz, 2 H), 2.35–2.26 (m, 1.5 H), 2.12–2.05 (m, 0.5 H), 1.70–1.41 (m, 4 H), 0.06 to –0.02 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 127.9, 127.0, 124.5, 123.3, 51.2, 50.9, 29.9, 29.2, 22.9, 22.8, 18.6, 17.9, –1.8, –1.6.

6-(Trimethylsilyl)hex-4-en-1-amine (58)

To a solution of **57** (321 mg, 1.63 mmol) in anhyd Et_2O (10 mL) was added $LiAlH_4$ (123 mg, 3.25 mmol) under argon at 0 °C. The solution was allowed to warm to r.t. and stirred for 3 h, then quenched by the addition of H_2O (120 μL), 15% aq NaOH (120 μL), and then H_2O (370 μL). The suspension was stirred for 1 h, then filtered over a Celite pad and concentrated to give **58** as a colorless oil (251 mg, 90%, 70:30 *E*/*Z*), which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.57–5.33 (m, 1 H), 5.31–5.13 (m, 1 H), 2.79–2.63 (m, 2 H), 2.22–2.08 (m, 1 H), 1.58–1.33 (m, 2 H), 0.07 to –0.02 (m, 9 H).

***N*-[6-(Trimethylsilyl)hex-4-enyl]but-3-enamide (59)**

But-3-enoic acid (0.27 mL, 3.15 mmol) was added to a solution of **58** (415 mg, 2.42 mmol) in anhyd CH_2Cl_2 (10 mL) in an ice bath. Then, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (604 mg, 3.15 mmol) and 1-hydroxybenzotriazole hydrate (65 mg, 0.48 mmol) were added and the solution was stirred at r.t. for 12 h. Sat. aq $NaHCO_3$ (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (pentane–EtOAc, 30:70) to give **59** (538 mg, 93%, 70:30 *E*/*Z*) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (ddt, *J* = 17.0, 10.3, 7.1 Hz, 1 H), 5.64 (br s, 1 H), 5.49–5.32 (m, 1 H), 5.29–5.12 (m, 3 H), 3.32–3.17 (m, 2 H), 2.98 (dt, *J* = 7.2, 1.6 Hz, 2 H), 2.28–1.95 (m, 2 H), 1.60–1.43 (m, 2 H), 1.42–1.23 (m, 2 H), 0.03 to –0.05 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 131.7, 127.5, 127.2, 119.5, 41.7, 39.2, 30.2, 29.8, 22.7, –1.9.

ESI-HMRS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{25}NOSi$: 240.1784; found: 240.1782.

3-(6-Oxooctahydro-2*H*-quinolizin-1-yl)propanal (63)

In a stainless steel autoclave under an inert atmosphere, a solution of $Rh(CO)_2acac$ (1.3 mg, 0.005 mmol) and biphephos (7.6 mg, 0.010 mmol) in anhyd degassed MeCN (3 mL) (prepared in a Schlenk glassware under an inert atmosphere) was added to a solution of **59** (58 mg, 0.242 mmol), camphorsulfonic acid (56 mg, 0.242 mmol) and few 4 Å molecular sieves in anhyd degassed MeCN (3 mL). The autoclave was flushed three times with H_2/CO (1:1). Then, the autoclave was filled with 500 kPa of H_2/CO (1:1) and was heated at 70 °C with stirring for 12 h. The autoclave was cooled to r.t. and the gases were slowly and carefully released. The reaction mixture was then concentrated under reduced pressure to give an oil. The residue was purified by flash chromatography (EtOAc–MeOH, 90:10) to give **63** (36 mg, 78%) as a colorless oil.

***trans*-Isomer**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (t, *J* = 1.4 Hz, 1 H), 4.81 (ddt, *J* = 13.1, 4.2, 2.1 Hz, 1 H), 2.98 (ddd, *J* = 9.4, 8.0, 5.8 Hz, 1 H), 2.55–2.33 (m, 3 H), 2.30–2.21 (m, 2 H), 2.15–2.08 (m, 1 H), 1.95–1.73 (m, 3 H), 1.72–1.66 (m, 1 H), 1.60 (m, 2 H), 1.44–1.26 (m, 3 H), 1.16–1.02 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.8, 169.4, 61.3, 42.7, 42.1, 40.8, 32.9, 30.2, 27.6, 25.0, 24.0, 19.0.

ESI-HMRS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{19}NO_2$: 210.1794; found: 210.1789.

9-Vinyloctahydro-4*H*-quinolizin-4-one (62)

In a stainless steel autoclave under an inert atmosphere, a solution of $Rh(CO)_2acac$ (1.2 mg, 0.004 mmol) and biphephos (10.5 mg, 0.013 mmol) in anhyd degassed MeCN (7 mL) (prepared in a Schlenk glassware under an inert atmosphere) was added to a solution of **59** (107 mg, 0.446 mmol) in anhyd degassed MeCN (7 mL). The autoclave was flushed three times with H_2/CO (1:1). Then, the autoclave was filled with 500 kPa of H_2/CO (1:1) and heated at 65 °C with stirring for 6 h. The autoclave was cooled to r.t. and the gases were slowly and carefully released. After degassing with argon, camphorsulfonic acid (56 mg, 0.242 mmol) was added and the reaction mixture was stirred at 65 °C for 4 h. After cooling, the mixture was then concentrated under reduced pressure to give an oil. The residue was purified by flash chromatography (EtOAc–MeOH, 95:5) to give **62** (52 mg, 65%) as a colorless oil.

***trans*-Isomer**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (ddd, *J* = 17.1, 10.2, 8.9 Hz, 1 H), 5.04–4.95 (m, 2 H), 4.77–4.70 (dm, *J* = 13.0 Hz, 1 H), 2.96 (dddd, *J* = 10.3, 7.4, 5.8 Hz, 1 H), 2.37–2.17 (m, 3 H), 1.95–1.84 (m, 2 H), 1.75–1.60 (m, 3 H), 1.56–1.26 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.7, 116.3, 60.3, 48.7, 42.7, 33.1, 32.1, 29.8, 28.1, 24.9, 18.8.

ESI-HMRS: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{17}NO$: 180.1388; found: 180.1388.

***trans*-6-Oxooctahydro-2*H*-quinolizine-1-carbaldehyde (64)**

To a solution of **62** (82 mg, 0.46 mmol) in anhyd CH_2Cl_2 (5 mL) and anhyd MeOH (2 mL) under argon at –78 °C was bubbled a stream of ozone until a light blue color was observed (saturation of O_3). The solution was flushed successively with O_2 and argon. Ph_3P (132 mg, 0.50 mmol) was added and the reaction mixture was allowed to reach r.t. and stirred for 4 h. The solvents were removed under reduced pressure and the residue was purified by column chromatography (EtOAc–MeOH, 98:2) to yield **64** (83 mg, 76%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (d, *J* = 2.8 Hz, 1 H), 4.82–4.77 (m, 1 H), 3.50 (ddd, *J* = 10.4, 8.0, 5.5 Hz, 1 H), 2.42–2.24 (m, 4 H), 2.13–2.06 (m, 1 H), 2.03–1.98 (m, 1 H), 1.80–1.73 (m, 2 H), 1.68–1.57 (m, 1 H), 1.53–1.39 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.7, 169.7, 55.9, 55.4, 41.9, 32.8, 28.2, 25.5, 23.9, 18.7.

ESI-HMRS: *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{15}NO_2$: 182.1181; found: 182.1183

((1*R,9a*S**)-Octahydro-1*H*-quinolizin-1-yl)methanol [(±)-Epilupinine, 65]**

To a solution of **64** (63 mg, 0.35 mmol) in anhyd THF (6 mL) under argon at 0 °C was added $LiAlH_4$ (66 mg, 1.74 mmol). The solution was stirred at reflux for 5 h, then quenched by the addition of H_2O (65 μL), aq 15% NaOH (65 μL), and then H_2O (130 μL). The suspension was stirred for 1 h, then filtered over a Celite pad and concentrated. The residue was purified by flash chromatography [Et_2O (saturated with NH_3)–MeOH, 70:30] to give **65** (41 mg, 70%) as a white solid; mp 78–80 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.63 (d, *J* = 10.9, 3.7 Hz, 1 H), 3.51 (dd, *J* = 10.9, 5.9 Hz, 1 H), 2.48 (br s, 1 H), 2.83–2.73 (m, 2 H), 2.04–1.96 (m, 2 H), 1.90–1.80 (m, 2 H), 1.77–1.73 (m, 1 H), 1.70–1.63 (m, 3 H), 1.61–1.55 (m, 2 H), 1.42–1.35 (m, 1 H), 1.25–1.14 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.50, 64.49, 57.0, 56.7, 44.0, 29.8, 28.4, 25.6, 25.1, 24.6.

ESI-HMRS: *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{19}NO$: 170.1545; found: 170.1548.

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