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Preparation of α-Acetonylpiperidines from α-Allylated Heterocycles by a Bromocyclocarbamation Reaction

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2,6-Disubstituted (alkyl)(allyl)- and diallylpiperidines containing C=C bonds in different environments can be selectively transformed into α-acetonylpiperidines, including the alkaloid (±)-6-epipinidinone. The key step is the bromocyclocarbamation reaction of the *N*-Boc-protected α-allylheterocycle with *N*-bromosuccinimide. The bulky *tert*-butyl group on the piperidine ring can affect the diastereoselectivity of the cyclization by 1,5-asymmetric induction. The structure of one of the isolated diastereomers was established by X-ray single-crystal diffraction. The prepared bicyclic bromides were readily dehydrobrominated with *t*BuOK and the corresponding enols were hydrolyzed to α-acetonylpiperidine hydrochlorides. The method presented is convenient and simple to perform.

Introduction

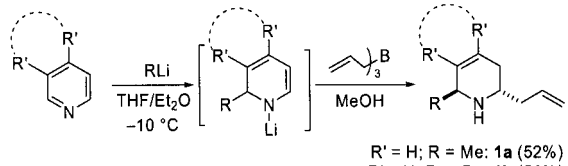
The piperidine ring is a ubiquitous structural motif in many naturally occurring compounds.[1] Moreover, piperidine alkaloids and their synthetic analogues are of great interest in the pharmaceutical industry because of their wide spectrum of biological activities.[2] For these reasons, and because the structural diversity of these alkaloids makes them a good vehicle for the testing of synthetic methodology, the stereocontrolled synthesis of piperidine derivatives has attracted considerable synthetic attention in the last few years.[3] One way to obtain the piperidine ring is to modify the corresponding pyridine or isoquinoline derivatives.

We have previously found that pyridines,[4] isoquinoline,[5] and pyrrole[6] undergo reductive *trans*-α,α′-diallylation on treatment with allylic boranes (triallyl-, trimethallyl, and tricrotylborane) and alcohol to give the corresponding α,α′-diallylated heterocyclic compounds. Furthermore, *gem*-α,α-diallylation can be achieved by reaction of triallylborane with nitriles, carboxylic acids, esters,[7] lactams,[8a] and amides,[8b] producing a wide range of allylated compounds. Successive treatment of pyridine and isoquinoline with alkyl- or phenyllithium, triallylborane, alcohol, and base lead to the formation of *trans*-α-(alkyl or phenyl)-α′-allyl-substituted heterocycles.[9a] Di- and monoallylated tetrahydropyridines thus obtained were used as starting materials for the preparation of bridged azabicycles[9c] and certain alkaloids such as epidihydropinidine, dihydropinidine, and indolizidines 167B and 209D.[9a,9b]

In this report we describe an approach to the preparation of piperidine-type amino ketones, including (±)-6-epipinidinone. Our approach is based on a simple and practical bromocyclocarbamation reaction of α-allyl-substituted heterocycles.

Results and Discussion

Three allylated heterocycles (**1a**–**c**) were prepared by a previously described protocol.[9a,9b] First organolithium (MeLi and *t*BuLi) was added to pyridine or isoquinoline (Scheme 1) at –10 °C. The resulting organolithium adducts were treated with triallylborane followed by MeOH in order to destroy the resulting amine–borane complex. The corresponding *trans*-6-alkyl-2-allyl-substituted heterocycles (**1a**–**c**) were isolated by either chromatography or distillation (for preparative experiments). The amines **1a**–**c** were treated with Boc_2O and the Boc-protected tetrahydropyridines were then subjected to a bromocyclocarbamation reaction with NBS (Scheme 2). This reaction was typically carried out in $CHCl_3$ under reflux for 1–1.5 h. The reaction mixture was



Scheme 1.

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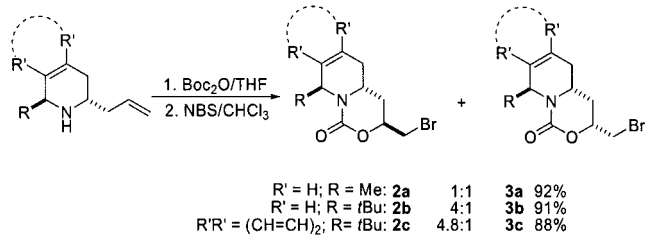
washed with 10% NaOH, filtered, and dried to afford analytically pure compounds **2** and **3** as a mixture of diastereomers.



Scheme 2.

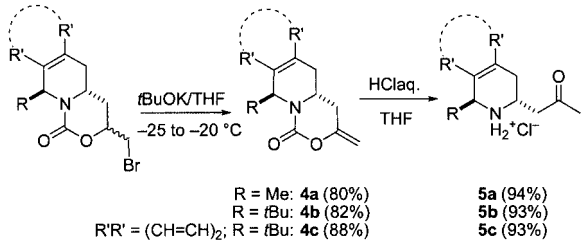
Earlier, a similar transformation (with iodine) was successfully exploited to protect the allyl group in 2,6-diallylated piperidine.[10a] The iodide was formed as a mixture of diastereomers in a 1:1 ratio. For this reason, this method was not selective enough for the synthesis of (–)-poranteridine.[10b] In the case of **1a**, bromocyclocarbamation also gave rise to an inseparable mixture of diastereomers (1:1).

It was not clear whether 1,3- or 1,5-induction was responsible for the stereoselectivity of the bromocarbamation reaction in the case of 2,6-disubstituted piperidines. Although a high level of 1,3-asymmetric induction is well known in halocyclization reactions of acyclic substrates,[11] the presence of an additional ring system has to be taken into account when estimating the expected level of stereoselectivity. Indeed when the substituent at the 2-position was bulky (**1b**, **1c**), a good level of diastereoselectivity was observed. We were able to separate the diastereomers (R = *t*Bu) and the structure of major isomer **2b** was unambiguously established by X-ray single-crystal crystallography (Figure 1).

The X-ray diffraction study revealed that **2b** is a bicyclic compound containing two six-membered rings in an unsymmetrical half-chair conformation with deviations of the C2, C3 and N1, C4 atoms, respectively, from the mean plane of the other ring atoms. Compound **2b** is chiral and has three asymmetric centers at the C2, C4, and C8 carbon atoms. The crystal of **2b** is a racemate with space group *Pbca*. The relative configurations of the asymmetric centers are (2*S**,4*R**,8*R**).

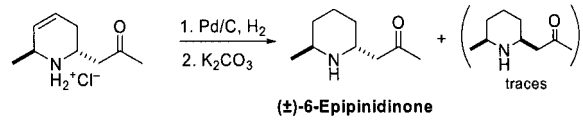
The difference in the isomeric ratio of the substituted isoquinoline derivative (**2c/3c** = 4.8:1) was more marked (Scheme 2). The structures of isomers **2c** and **3c** were assigned by analogy with **2b**. The observed diastereoselectivity can be rationalized on the basis of the analysis of the conformations of the six-membered chair-like transition state.[11]

We found that bromomethyl derivatives undergo rapid dehydrobromination (at –20 °C in minutes) with *t*BuOK in THF (Scheme 3). Cyclic enol esters obtained in this way have high analytical purity and can be converted directly into amino ketone hydrochlorides with HCl solution in high yields.



Scheme 3.

Note that a Wacker-type oxidation reaction[12] failed in our experiments, even when using protected (Bn, Cbz) tetrahydropyridines, as described in refs.[10a,13] Hydrogenation of compound **5a** gave rise to alkaloid (±)-6-epipinidinone, a racemic form of the naturally occurring (+)-6-epipinidinone [or (2*R*,6*S*)-2-methyl-6-(2-oxopropyl)piperidine] (Scheme 4),



Scheme 4.

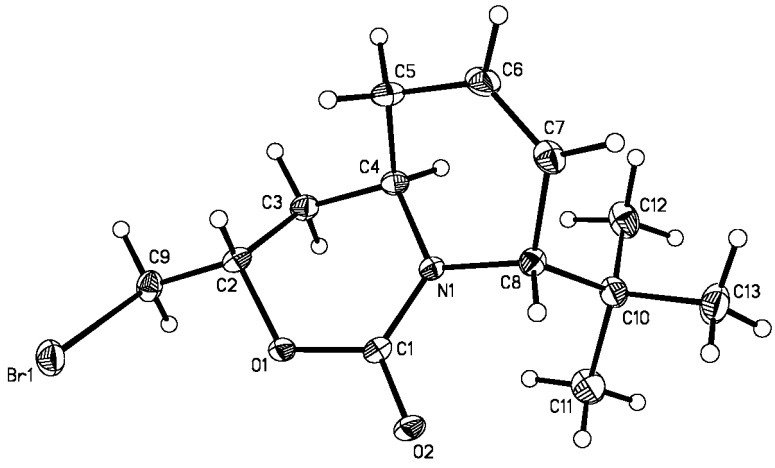
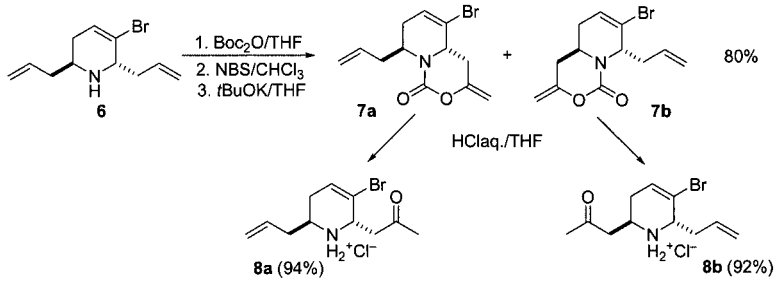


Figure 1. Molecular structure of **2b**. The non-hydrogen atoms are shown with the thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms have been drawn as circles of arbitrarily small radius for clarity.



Scheme 5.

which together with its *cis* isomer are trace components in extracts of *Picea Pungens* Engelm (Colorado blue spruce);[14a] both isomers are also the components of alkaloids isolated from coccinellid (*Cryptolaemus montrouzieri*).[14b] It was noted that the *trans* isomer underwent spontaneous isomerization during isolation to the *cis* isomer and actually has to be the major or even sole isomer found in intact ladybird beetles. We also observed a little isomerization of the *trans* ketone to its *cis* isomer during isolation of its free base (after treatment of its hydrochloride salt with K_2CO_3), as detected by ^{1}H NMR spectroscopy. The *cis*/*trans* isomerization process is evidently a general process in α-acetonylpiperidines and also occurs in lobeline.[14c,14d]

In addition, *trans*-2,6-diallyl-5-bromo-1,2,3,6-tetrahydropyridine (**6**) was subjected to the bromocyclocarbamation reaction (Scheme 5). The protection of **6** and subsequent cyclization reaction were performed without isolation of the intermediates. After dehydrohalogenation, two isomers **7a** and **7b** were isolated by flash chromatography. These isomers were structurally discriminated by NMR spectroscopy (COSY and NOESY experiments). We observed no selectivity in the bromocyclocarbamation reaction; however, the two allyl groups were shown to have slightly different reactivities. The composition of the cyclic enol esters obtained after dehydrohalogenation was equal to 1:1.8 in favor of **7a**. Additionally, we detected the formation of the free base of amino ketone **7a**′ derived from **7a**. The corresponding enol ester is probably very prone to hydrolytic cleavage which occurs during the chromatography or TLC monitoring steps.

After individual hydrolytic treatment of the enol esters **7a** and **7b** with HCl solution, both amino ketone hydrochlorides **8a** and **8b** were isolated in good yields.

Conclusion

A simple and fast strategy for the conversion of α,α′-diallyl- and α-alkyl-α′-allyl-tetrahydropyridines and -isoquinoline into the corresponding amino ketone hydrochlorides has been elaborated. In this way the alkaloid (±)-6-epipinidinone was prepared. It was found that substituents on the piperidine ring can affect the diastereoselectivity of the halocyclocarbamation reaction by 1,5-asymmetric induction. Additionally, this transformation does not affect other double bonds in the molecule.

Experimental Section

General: The manipulations with triallylborane were carried out under dry argon. Triallylborane[15] and compounds **1a**[9a] and **6**[4c] were prepared as described previously. NMR spectra were recorded with Bruker AMX-400 and Avance-300 instruments. Chemical shifts δ are given in ppm and coupling constants J in Hz. Mass spectra were recorded with a Finnigan Polaris Q Ion Trap spectrometer. Column chromatography was carried out using silica gel (Merck, 60–230 mesh). Thin-layer chromatography was performed on silica gel 60 F_{254} (Merck). All compounds were prepared in racemic form.

(2*S,6*R**)-2-Allyl-6-(*tert*-butyl)-1,2,3,6-tetrahydropyridine (1b):** Dry pyridine (1.22 g/1.25 mL, 15 mmol) in Et_2O (1 mL) was added to a solution of *t*BuLi (0.85 M in pentane, 20 mL, 17 mmol) in Et_2O/THF (1:1) (12 mL) at –10 °C and the resulting solution was stirred at –5 to 0 °C for 2 h. Then neat triallylborane (2.41 g/3.1 mL, 18 mmol) was added to the mixture at –15 °C and stirring was continued for 10 min followed by the addition of MeOH (10 mL) at 0 °C. The mixture was refluxed for 1 h and then 5 N NaOH (10 mL, 50 mmol) was added to complete the deboronation process. The organic layer was separated and the aqueous layer extracted with hexane (20 mL). The combined organic phases were dried with K_2CO_3, the solvent was evaporated, and the residue was purified by FC (hexane/EtOAc, 2:1) on silica gel, R_f = 0.54. Yield: 1.5 g (56%) as a reddish liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.80–5.67 (m, 3 H), 5.09–5.00 (m, 2 H), 3.02–2.96 (m, 2 H), 2.20–2.10 (m, 3 H), 1.72 (m, 1 H), 0.83 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.01, 126.64, 125.40, 117.07, 59.25, 48.90, 39.00, 35.15, 30.49, 26.68 (3 CH_3) ppm. MS (70 eV, EI): *m*/*z* (%) = 180.2 (2) $[MH]^+$, 164 (7), 138 (6), 122 (20), 108 (7), 93 (9), 81 (12), 80 (100), 79 (8), 67 (8), 53 (5). $C_{12}H_{21}N$ (179.3): calcd. C 80.36, H 11.81, N 7.81; found C 80.32, H 11.69, N 7.77.

(1*S,3*S**)-3-Allyl-1-(*tert*-butyl)-1,2,3,4-tetrahydroisoquinoline (1c):** The procedure was the same as that used for the preparation of **1b**, but was carried out with isoquinoline. Isolation by FC (hexane/EtOAc, 5:1) on silica gel, R_f = 0.56. Yield: 2.2 g (64%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.12 (m, 4 H), 5.97–5.83 (m, 1 H), 5.18–5.13 (m, 2 H), 3.78 (s, 1 H), 3.54 (m, 1 H), 3.00 (dd, J = 5.3, 16.2 Hz, 1 H), 2.60 (dd, J = 7.8, 16.2 Hz, 1 H), 2.22 (m, 1 H), 2.11 (m, 1 H), 1.04 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.7, 135.6, 135.3, 129.03, 128.48, 126.15, 124.55, 117.57, 63.38, 48.07, 41.62, 37.71, 34.96, 28.63 (3 CH_3) ppm. MS

(70 eV, EI): *m*/*z* (%) = 230.2 (6) $[MH]^+$, 188 (5), 173 (13), 172 (94), 155 (5), 143 (7), 131 (16), 130 (100), 117 (4), 103 (5), 91 (2), 77 (4). $C_{16}H_{23}N$ (229.4): calcd. C 83.79, H 10.11, N 6.11; found C 83.62, H 10.18, N 6.09.

General Protocol for the Protection/Bromocyclocarbamation Process: Amines **1a**–**c** or **6** (1 equiv.) and Boc_2O (1.05 equiv.) in THF (2 mL for 4 mmol) were refluxed for 1–2 h (TLC control). After completion of the reaction, THF was evaporated, residual oil was dissolved in $CHCl_3$, NBS (1.2 equiv.) was added, and the mixture refluxed for 1 h (TLC control). The solvent was evaporated and the residue was treated with Et_2O (10 mL for 4 mmol) and 10% NaOH (5 mL for 4 mmol) with stirring for 15 min. The organic layer was separated, dried with K_2CO_3, and the solvent evaporated.

(4a*R,8*S**)-3-(Bromomethyl)-8-methyl-4,4a,5,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one (2a/3a):** Yield: 2.76 g (92%). R_f = 0.43 (hexane/EtOAc, 1:1). Diastereoisomeric ratio = 1:1, estimated by ^1H NMR spectroscopy. MS (70 eV, EI): *m*/*z* (%) = 260/262 (4) $[MH]^+$, 244/246 (27), 200/202 (25), 180 (55), 138 (19), 120 (100), 94 (44), 80 (22), 67 (16), 39 (10). $C_{10}H_{14}BrNO_2$ (260.1): calcd. C 46.17, H 5.42, Br 30.72, N 5.38; found C 46.32, H 5.56, Br 30.74, N 5.29.

(3*S,4a*R**,8*R**)-3-(Bromomethyl)-8-(*tert*-butyl)-4,4a,5,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one (2b) and (3*R**,4a*R**,8*R**)-3-(Bromomethyl)-8-(*tert*-butyl)-4,4a,5,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]-oxazin-1-one (3b):** Total yield: 0.83 g (91.2%). Diastereomeric ratio = 1:4, estimated by ^1H NMR spectroscopy. The individual isomers were isolated by FC (hexane/EtOAc, 3:1) on silica gel: **2b** as white crystals, m.p. 137–138 °C; **3b** as an oil.

2b: R_f = 0.62 (hexane/EtOAc, 2:1) (major isomer). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.88 (ddt, *J* = 1.8, 5.5, 12.3 Hz, 1 H, C*H*=CH_2), 5.81 (m, 1 H, C*H*=CHN), 4.56 (m, 1 H, C*H*N*t*Bu), 4.49 (m, 1 H, CHO), 3.89 (m, 1 H, C*H*NCH_2), 3.58 (dd, *J* = 4.4, 10.5 Hz, 1 H, CH_aH_bBr), 3.42 (dd, *J* = 7.3, 10.5 Hz, 1 H, CH_aH_bBr), 2.28–1.98 (m, 4 H), 1.02 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.55 (C=O), 126.36 (CH=), 124.89 (CH=), 71.18, 62.17, 47.34, 36.97, 32.85, 31.67, 30.06, 27.97 (3 CH_3) ppm. MS (70 eV, EI): *m*/*z* (%) = 302/304 (7) $[MH]^+$, 244/246 (32), 200/202 (26), 166 (89), 120 (100), 88 (20), 80 (50), 79 (30), 67 (5), 44 (15). $C_{13}H_{20}BrNO_2$ (302.2): calcd. C 51.67, H 6.67, Br 26.4, N 4.63; found C 51.55, H 6.76, Br 26.53, N 4.59.

3b: R_f = 0.71 (hexane/EtOAc, 2:1) (minor isomer). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.86 (m, 2 H, CH=), 4.68 (m, 1 H, C*H*N*t*Bu), 4.41 (dddd, *J* = 1.6, 4.6, 7.1, 11.4 Hz, 1 H, CH), 3.83 (dddd, *J* = 3.9, 7.5, 10.5, 10.5 Hz, 1 H, CH), 3.60 (dd, *J* = 4.6, 10.5 Hz, 1 H, CH_aH_bBr), 3.44 (dd, *J* = 7.1, 10.7 Hz, 1 H, CH_aH_bBr), 2.61 (ddd, *J* = 3.0, 7.3, 13.7 Hz, 1 H), 2.32 (ddd, *J* = 3.5, 3.6, 16.4 Hz, 1 H), 1.97 (ddd, *J* = 2.7, 10.5, 18.0 Hz, 1 H), 1.64 (ddd, *J* = 10.9, 21.9, 10.5 Hz, 1 H), 1.02 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.27, 125.22, 123.70, 72.76, 59.80, 48.86, 37.78, 34.58, 33.37, 32.21, 27.76 (3 CH_3) ppm. MS (70 eV, EI): *m*/*z* (%) = 302/304 (1) $[MH]^+$, 244/246 (25), 200/202 (23), 166 (65), 120 (100), 88(17), 80 (41), 79 (24), 53 (7), 44 (12). $C_{13}H_{20}BrNO_2$ (302.2): calcd. C 51.67, H 6.67, N 4.63; found C 51.48, H 6.83, N 4.55.

(3*S,4a*R**,10*S**)-3-(Bromomethyl)-10-(*tert*-butyl)-4,4a,5,10-tetrahydro-3*H*-[1,3]oxazino[3,4-*b*]isoquinolin-1-one (2c) and (3*R**,4a*R**,10*S**)-3-(Bromomethyl)-10-(*tert*-butyl)-4,4a,5,10-tetrahydro-3*H*-[1,3]oxazino[3,4-*b*]isoquinolin-1-one (3c):** Total yield: 1.29 g (88%). Diastereomeric ratio = 1:4.8, as estimated by ^1H NMR spectroscopy. The individual isomers were isolated by FC (hexane/EtOAc, 3:1) on silica gel: **2c** as white crystals, m.p. 147–148 °C; **3c** as an oil.

2c: R_f = 0.51 (hexane/EtOAc, 3:1) (major isomer). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.15 (m, 3 H, Ar), 7.09 (d, *J* = 7.1 Hz, 1 H, Ar), 5.34 (s, 1 H, C*H*t*Bu), 4.50 (dddd, *J* = 2.0, 4.6, 7.3, 8.9 Hz, 1 H, C*H*NCH_2), 4.24 (dddd, *J* = 5.3, 7.1, 7.6, 10.7 Hz, 1 H, C*H*O), 3.57 (dd, *J* = 4.4, 10.5 Hz, CH_aH_bAr), 3.38 (dd, *J* = 7.3, 10.5 Hz, CH_aH_bAr), 3.32 (dd, *J* = 7.5, 17.4 Hz, 1 H, CH_aH_bBr), 2.73 (dd, *J* = 7.1, 17.1 Hz, 1 H, CH_aH_bBr), 2.57 (ddd, *J* = 2.1, 5.0, 13.5 Hz, 1 H, CH_aH_bCHO), 1.71 (ddd, *J* = 11.2, 11.4, 13.2 Hz, 1 H, CH_aH_bCHO), 1.03 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.29, 134.41, 131.76, 128.51, 128.24, 127.21, 125.57, 73.98, 62.46, 48.16, 38.26, 35.64, 34.97, 32.60, 28.61 (3 CH_3) ppm. MS (70 eV, EI): *m*/*z* (%) = 352/354 (0.5) $[MH]^+$, 294/296 (95), 250/252 (98), 214/216 (15), 170 (100), 143 (12), 130 (57), 103 (12), 77 (5). $C_{17}H_{22}BrNO_2$ (352.3): calcd. C 57.96, H 6.29, Br 22.68, N 3.98; found C 57.99, H 6.15, Br 22.83, N 3.97.

3c: R_f = 0.55 (hexane/EtOAc, 3:1) (minor isomer). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.14 (m, 3 H, Ar), 7.11 (d, *J* = 7.4 Hz, 1 H, Ar), 5.27 (s, 1 H, C*H*t*Bu), 4.48 (m, 1 H, C*H*NCH_2), 4.24 (ddd, *J* = 2.2, 8.3, 14.2 Hz, 1 H, C*H*O), 3.59 (dd, *J* = 4.3, 10.5 Hz, 1 H, CH_aH_bAr), 3.45 (dd, *J* = 7.2, 10.5 Hz, 1 H, CH_aH_bAr), 2.92 (d, *J* = 8.4 Hz, 2 H, CH_2Br), 2.19 (ddd, *J* = 6.1, 10.4, 14.0 Hz, 1 H, CH_aH_bCHO), 2.14 (dt, *J* = 2.2, 14.0 Hz, CH_aH_bCHO), 1.06 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.54, 135.09, 132.49, 128.98, 128.02, 126.93, 125.86, 71.09, 62.68, 45.99, 37.34, 34.78, 32.57, 30.66, 29.24 (3 CH_3) ppm. MS (70 eV, EI): *m*/*z* (%) = 352/354 (0.5) $[MH]^+$, 244/246 (40), 200/202 (30), 166 (70), 120 (100), 80 (42), 77 (10), 44 (10).

Typical Dehydrohalogenation with *t*BuOK: A mixture of diastereomeric bromides **2** (1 equiv.) was dissolved in THF (6 mL for 3 mmol). The solution was kept at –25 to –20 °C and *t*BuOK (1.2 equiv.) was added. The pink mixture was stirred for 5 min and then the solution was passed through a short pad of silica gel to remove colored organic material from the solution. The silica gel pad was washed with a mixture of hexane/EtOAc, 2:1. Concentration of the colorless filtrate under reduced pressure afforded the analytically pure product.

(4a*R,8*S**)-8-Methyl-3-methylene-4,4a,5,8-tetrahydro-3*H*-pyrido-[1,2-*c*][1,3]oxazin-1-one (4a):** Yield: 0.53 g (84%) as an oil. R_f = 0.67 (hexane/EtOAc, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.75 (ddt, *J* = 1.9, 5.7, 10.2 Hz, 1 H CH=), 5.65 (dtd, *J* = 0.9, 2.6, 10.2 Hz, 1 H CH=), 4.72 (s, 1 H), 4.70 (m, 1 H), 4.34 (s, 1 H), 3.61 (ddd, *J* = 3.7, 6.7, 14.5 Hz, 1 H), 2.79 (dd, *J* = 6.6, 14.4 Hz, 1 H), 2.42 (dd, *J* = 3.7, 14.4 Hz, 1 H), 2.20 (dddd, *J* = 2.5, 4.6, 11.1, 17.0 Hz, 1 H), 2.02 (ddd, *J* = 3.8, 4.7, 17.0 Hz, 1 H), 1.27 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.24 (C=O), 129.85 (CH=), 123.27 (CH=), 94.78 (C=), 50.21 (CH), 45.23 (CH), 31.20 (CH_2), 31.06 (CH_2), 28.16 (CO=), 18.53 (CH_3) ppm. MS (70 eV, EI): *m*/*z* (%) = 179 (42) $[M]^+$, 164 (100), 134 (14), 122 (19), 104 (12); 94 (30), 80 (33), 67 (22). $C_{10}H_{13}NO_2$ (179.2): calcd. C 67.02, H 7.31, N 7.82; found C 66.95, H 7.28, N 7.90.

(4a*R,8*R**)-8-(*tert*-Butyl)-3-methylene-4,4a,5,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one (4b):** Yield: 0.36 g (82%) as an oil. R_f = 0.56 (hexane/EtOAc, 2:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.91 (ddt, *J* = 1.8, 5.7, 10.5 Hz, 1 H CH=), 5.65 (dtd, *J* = 0.9, 2.5, 10.5 Hz, 1 H, CH=), 4.70 (s, 1 H, CH_aH_b=), 4.50 (m, 1 H, C*H*N*t*Bu), 4.29 (t, *J* = 1.6 Hz, 1 H, CH_aH_b=), 3.76 (m, 1 H, CHN), 2.85 (dd, *J* = 6.4, 14.4 Hz, 1 H, CH_aH_bCO=), 2.42 (dd, *J* = 2.0, 14.4 Hz, 1 H, CH_aH_bCO=), 2.19 (dddd, *J* = 2.5, 4.8, 11.4, 16.9 Hz, 1 H, CH_aH_bCH=), 1.96 (ddd, *J* = 4.1, 5.3, 17.1 Hz, CH_aH_bCH=), 1.03 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.89, 150.27, 125.83, 125.60, 94.29, 63.21, 47.51, 36.47, 30.28, 27.73 (3 CH_3) ppm. MS (70 eV, EI): *m*/*z* (%) = 222 (40) $[MH]^+$, 206 (10)

$[M - CH_3]^+$, 165 (100), 164 (62), 150 (10), 124 (17), 120 (42), 104 (18), 91 (26), 80 (65), 67 (10), 53 (6). $C_{13}H_{19}NO_2$ (221.3): calcd. C 70.56, H 8.65, N 6.33; found C 70.58, H 8.54, N 6.28.

(4a*R,10*S**)-10-(*tert*-Butyl)-3-methylene-4,4a,5,10-tetrahydro-3*H*-[1,3]oxazino[3,4-*b*]isoquinolin-1-one (4c):** Yield: 0.69 g (88%) as an oil. R_f = 0.46 (hexane/EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.14 (m, 3 H, Ar), 7.11 (d, J = 7.1 Hz, 1 H, Ar), 5.27 (s, 1 H, CH*t*Bu), 4.71 (s, 1 H, CH_aH$_b$=), 4.29 (s, 1 H, CH$_a$$H_b$=), 4.16 (m, 1 H, C*H*N), 3.03 (dd, J = 6.4, 16.7 Hz, 1 H), 2.84 (dd, J = 8.6, 16.7 Hz, 1 H), 2.80 (dd, J = 5.2, 14.3 Hz, 1 H), 2.42 (dd, J = 5.8, 14.3 Hz, 1 H), 1.07 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.03, 150.78, 135.05, 132.43, 128.93, 128.47, 127.12, 125.83, 93.91, 63.79, 47.25, 37.69, 33.62, 32.50, 28.93 (3 CH_3) ppm. MS (70 eV, EI): *m*/*z* (%) = 272 (8) $[M + H]^+$, 256 (5), 214 (100), 170 (28), 141 (15), 130 (34), 128 (10), 115 (5), 103 (5), 77 (4). $C_{17}H_{21}NO_2$ (271.3): calcd. C 75.25, H 7.80, N 5.16; found C 75.22, H 7.74, N 5.18.

Typical Hydrolysis Procedure: The corresponding enol ester **4** (1 equiv.) was dissolved in THF/*i*PrOH (9 mL:1 mL for 2 mmol) and then a 6 N HCl solution (5 equiv.) was added. The resulting solution was refluxed for 30 min. After completion of the reaction (TLC control) the reaction mixture was concentrated under reduced pressure to dryness, diethyl ether was added to the residue, and the mixture was stirred until complete crystallization of the amino ketone hydrochloride. The precipitate was filtered off and dried in vacuo.

(2*R,6*S**)-6-Methyl-2-(2-oxopropyl)-1,2,3,6-tetrahydropyridinium Hydrochloride (5a):** Yield: 0.65 g (94%), m.p. 159–160 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.88 (br. s, 1 H, NH_2), 9.29 (br. s, 1 H NH_2), 5.79 (br. d, J = 10.5 Hz, 1 H), 5.68 (br. d, J = 10.5 Hz, 1 H), 3.85 (br. s, 1 H), 3.68 (br. s, 1 H), 3.15 (dd, J = 4.6, 18.0 Hz, 1 H), 2.90 (dd, J = 8.0, 18.0 Hz, 1 H), 2.38 (br. d, J = 18.3 Hz, 1 H), 2.17 (s, 3 H), 2.15–2.06 (br. m, 1 H), 1.36 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 205.76 (C=O), 126.54 (CH=), 124.21 (CH=), 47.20, 44.56, 44.12, 30.68, 27.29, 17.99 ppm. MS (70 eV, EI): *m*/*z* (%) = 189 (4) $[M]^+$, 154 (20) $[M - Cl]^+$, 138 (6), 110 (6), 95 (25), 94 (100), 80 (83), 67 (21), 53 (10), 39 (10). $C_9H_{16}ClNO$ (189.7): calcd. C 56.99, H 8.50, Cl 18.69, N 7.38; found C 56.82, H 8.56, Cl 18.74, N 7.29.

(2*S,6*R**)-2-Methyl-6-(2-oxopropyl)hexahydropyridinium Hydrochloride [(±)-6-Epipinidinone Hydrochloride]:** A solution of **5a** (0.38 g, 2.0 mmol) in MeOH (10 mL) and palladium on carbon (10%, 0.2 g) were successively added to a steel autoclave. The resulting solution was hydrogenated at 580 psi at 40 °C with rotation for 4 h. After filtration, the resulting clear solution was concentrated under reduced pressure and the residue was treated with EtOAc containing some $CHCl_3$. The precipitate was collected and dried in vacuo to afford 0.32 g (85%) of (±)-6-epipinidinone hydrochloride, m.p. 69–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.12 (br. s, 1 H), 8.69 (br. s, 1 H), 3.44 (br. m, 1 H), 3.14 (m, 1 H), 2.92 (dd, J = 4.2, 18.4 Hz, 1 H), 2.57 (dd, J = 8.4, 18.4 Hz, 1 H), 1.84 (s, 3 H), 1.62–1.55 (m, 2 H), 1.35–1.24 (m, 4 H), 1.08 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.58, 48.04, 46.69, 43.72, 30.26, 28.13, 26.64, 17.07, 16.39 ppm. $C_9H_{18}ClNO$ (191.7): calcd. C 56.39, H 9.46, Cl 18.49, N 7.31; found C 56.18, H 9.44, Cl 18.54, N 7.26. The ^{1}H NMR spectrum of the free base of the alkaloid is consistent with literature data.[14a] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.53 (m, 1 H), 3.12 (m, 1 H), 2.83 (dd, J = 7.8, 17.2 Hz, 1 H), 2.57 (dd, J = 5.5, 17.2 Hz, 1 H), 2.16 (s, 3 H), 1.73–1.60 (m, 2 H), 1.59–1.51 (m, 1 H), 1.39–1.27 (m, 3 H), 1.16 (d, J = 6.5 Hz, 3 H) ppm.

(2*R,6*R**)-6-(*tert*-Butyl)-2-(2-oxopropyl)-1,2,3,6-tetrahydropyridinium Hydrochloride (5b):** Yield: 0.31 g (93%), m.p. 183–184 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.23 (br. s, 1 H NH_2), 8.39 (br. s, 1 H NH_2), 5.96 (br. d, J = 10.7 Hz, 1 H, C*H*=CH$_2$), 5.68 (d, J = 10.7 Hz, 1 H, C*H*=CH*t*Bu), 4.12 (br. s, 1 H, C*H*NCH$_2$), 3.58 (d, J = 16.0 Hz, 1 H, CH_aH$_b$CH=), 3.49 (br. s, 1 H, CH*t*Bu), 2.83 (dd, J = 8.2, 17.3 Hz, 1 H, CH$_a$$H_b$CH=), 2.75 (d, J = 18.1 Hz, 1 H, CH_aH$_b$CO), 2.27 (d, J = 18.1 Hz, 1 H, CH$_a$$H_b$CO), 2.23 (s, 3 H, CH_3), 1.17 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.86 (C=O), 125.97 (*C*H=CH$_2$), 121.62 (*C*H=Ch*t*Bu), 59.67 (*C*h*t*Bu), 47.16 (*C*HCH$_2$), 43.29 (*C*H$_2$CH=), 34.41 (C), 30.38 (CH_3), 26.75 (3 CH_3), 26.04 (*C*H$_2$C=O) ppm. MS (70 eV, EI): *m*/*z* (%) = 231 (0.1) $[M]^+$, 196 (10), 138 (15), 122 (7), 80 (100), 78 (4), 53 (3). $C_{12}H_{22}ClNO$ (231.8): calcd. C 62.19, H 9.57, Cl 15.30, N 6.04; found C 62.04, H 9.67, Cl 15.43, N 6.04.

(1*S,3*R**)-1-(*tert*-Butyl)-3-(2-oxopropyl)-1,2,3,4-tetrahydroisoquinolinium Hydrochloride (5c):** Yield: 0.56 g (93%), m.p. 155–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.62 (br. s, 1 H, NH), 8.58 (br. s, 1 H, NH), 7.27–7.23 (m, 2 H, Ar), 7.18 (dd, J = 2.1, 8.6 Hz, 1 H, Ar), 7.12 (dd, J = 1.9, 8.3 Hz, 1 H, Ar), 4.72 (br. s, 1 H, CHN), 4.33 (t, J = 4.5 Hz, 1 H, C*H*t*Bu*), 3.39 (dd, J = 2.8, 18.3 Hz, 1 H), 3.25 (dd, J = 4.0, 16.6 Hz, 1 H), 2.87 (dd, J = 2.5, 16.6 Hz, 1 H), 2.30 (dd, J = 9.2, 18.3 Hz, 1 H), 2.06 (s, 3 H, CH_3), 1.17 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.68 (C=O), 132.29, 129.80, 129.64, 128.72, 128.19, 126.41, 62.92, 47.48, 42.79, 36.90, 31.24, 30.37, 26.93 ppm. MS (70 eV, EI): *m*/*z* (%) = 281 (0.3) $[M]^+$, 188 (38), 131 (15), 130 (100), 129 (10), 103 (10), 77(5). $C_{16}H_{24}ClNO$ (281.8): calcd. C 68.19, H 8.58, Cl 12.58, N 4.97; found C 68.08, H 8.66, Cl 12.62, N 5.02.

(4a*S,8*S**)-8-Allyl-5-bromo-3-methylene-4,4a,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one (7a) and (4a*R**,8*S**)-8-Allyl-7-bromo-3-methylene-4,4a,5,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one (7b):** A mixture of four diastereoisomeric dibromides (0.72 g, 1.97 mmol) in THF (4 mL), obtained from **6** (0.5 g, 2.06 mmol) in a total yield of 96% according to the above-mentioned protocols was dehydrohalogenated with *t*BuOK (0.26 g, 2.36 mmol) at –20 °C for 5 min. After standard treatment, the product mixture was purified by FC on silica gel (hexane/EtOAc, 4:1). Three fractions were isolated as oils: first **7a** (0.22 g), second **7b** (0.16 g), and third amino ketone **7a′** derived from **7a** (0.07 g) in a total yield of 80%.

7a: Major fraction. R_f = 0.43 (hexane/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.15 (dm, J = 7.0 Hz, 1 H, CH=$_{cycle}$), 5.72 (m, 1 H, CH=$_{allyl}$), 5.06–5.01 (m, 2 H, CH_2=), 4.71 (dd, J = 7.2, 14.4 Hz, 1 H, C*H*NCH$_2$), 4.63 (m, 1 H, CH_aH$_b$=C), 4.28 (m, 1 H, CH$_a$$H_b$=C), 3.94 (dm, J = 12.0 Hz, 1 H, C*H*NCBr=), 3.13 (dd, J = 3.6, 14.2 Hz, 1 H, CH_aH$_b$CHN.Br), 2.45 (dddd, J = 2.2, 3.6, 6.1, 17.5 Hz, 1 H, CH_aH$_b$CH=$_{cycle}$), 2.35–2.18 (m, 3 H, CH$_a$$H_b$CHN.Br and C$H_2CHN_{chain}$), 2.06 (dddd, J = 1.0, 2.1, 7.0, 17.6 Hz, 1 H, CH$_a$$H_b$CH=$_{cycle}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.26 (C), 150.00 (C), 134.13 (CH=$_{allyl}$), 127.49 (CH=$_{cycle}$), 118.65 CH$_2$=$_{allyl}$), 118.32 (CBr), 93.85 (CH$_2$=C), 52.62 (*C*HNCBr), 47.98 (*C*HNCH$_2$), 36.05 (CH$_{2\ chain}$), 32.34 (*C*H$_2$CHN.Br), 29.91 (CH$_{2\ in\ cycle}$) ppm. $C_{12}H_{14}BrNO_2$ (284.2): calcd. C 50.72, H 4.97, Br 28.12, N 4.93; found C 50.69, H 4.86, Br 27.95, N 4.82.

7b: Minor fraction. R_f = 0.31 (hexane/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.07 (m, 1 H, CH=$_{cycle}$), 5.84–5.73 (m, 1 H, CH=$_{all}$), 5.08–5.02 (m, 2 H, CH$_2$=$_{all}$), 4.85 (dm, J = 8.1 Hz, 1 H, C*H*NAll), 4.70 (s, 1 H, CH_aH$_b$=C), 4.30 (m, 1 H, CH$_a$$H_b$=C), 3.68 (m, 1 H, C*H*NCH$_2$C=), 2.79 (dm, J = 14.7 Hz, 1 H, CH_aH$_{b\ in\ allyl}$), 2.70 (ddd, J = 0.9, 6.2, 14.6 Hz, 1 H, CH_aH$_b$CO=), 2.40 (ddd, J = 7.5, 8.6, 14.9 Hz, 1 H, CH$_a$$H_{b\ in\ allyl}$), 2.34 (dd, J = 2.6, 14.3 Hz, 1 H, CH$_a$$H_b$CO=), 2.26 (dddd, J = 2.2, 4.3, 11.4,

16.8 Hz, 1 H, CH_aH$_b$CH=$_{\text{in cycle}}$), 2.03 (dt, J = 4.8, 17.1 Hz, 1 H, CH$_a$$H_b$CH=$_{\text{in cycle}}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.79 and 149.59 (C=O and C=CH$_2$), 133.47 (CH=$_{\text{all}}$), 127.07 (CH=$_{\text{cycle}}$), 121.54 (CBr=), 118.28 (CH$_2$=$_{\text{all}}$), 95.71 (CH$_2$=C), 58.64 (CHNAll), 44.98 (CHNCH$_2$C=), 35.98 (CH$_2$All), 33.13 (CH$_{2\text{ in cycle}}$), 30.18 (CH$_2$CO) ppm. MS (70 eV, EI): m/z (%) = 283/285 (0.4) [M]$^+$, 242/244 (100/95), 198/200 (34), 169/171 (10), 158/160 (20), 119 (35), 118 (75), 91 (27). $C_{12}H_{14}BrNO_2$ (284.2): calcd. C 50.72, H 4.97, Br 28.12, N 4.93; found C 50.66, H 4.95, Br 28.03, N 4.87.

1-[(2*S,6*S**)-6-Allyl-3-bromo-1,2,5,6-tetrahydro-2-pyridinyl]acetone (7a′):** R_f = 0.24 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.10 (m, 1 H, CH=$_{\text{cycle}}$), 5.75 (qt, J = 7.1, 10.3, 16.7 Hz, 1 H, CH=$_{\text{a11}}$), 5.11 (d, J = 6.2 Hz, 1 H, CH_aH$_b$=), 5.07 (s, 1 H, CH$_a$$H_b$=), 3.96 (d, J = 10.3 Hz, 1 H, CHN), 2.96 (dd, J = 2.7, 16.9 Hz, 1 H, CH_aH$_b$C=O), 2.89 (m, 1 H, CHNAll), 2.74 (dd, J = 10.0, 16.9 Hz, 1 H, CH$_a$$H_b$C=O), 2.20 (s, 3 H, CH$_3$), 2.15 (t, J = 7.3 Hz, 2 H, CH$_{2\text{ all}}$), 2.06 (m, 1 H, CH_aH$_b$CH=$_{\text{cycle}}$), 1.92 (ddt, J = 2.5, 9.2, 17.4 Hz, 1 H, CH$_a$$H_b$CH=$_{\text{cycle}}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.59, 134.62, 128.66, 123.78, 117.73, 55.40, 45.87, 45.53, 39.77, 34.26, 30.71 ppm.

For details of the hydrolysis procedure, see above.

(2*S,6*S**)-2-Allyl-5-bromo-6-(2-oxopropyl)-1,2,3,6-tetrahydropyridinium Hydrochloride (8a):** Yield: 0.19 g (94%) as cream-colored crystals, m.p. 179–182 °C (dec.). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.22 and 9.43 (br. s, 1 H each, NH$_2^+$), 6.32 (m, 1 H, CH=$_{\text{cycle}}$), 5.84–5.71 (m, 1 H, CH=$_{\text{allyl}}$), 5.24–5.16 (m, 2 H, CH$_2$=$_{\text{allyl}}$), 4.45 (dm, J = 5.7 Hz, 1 H, CHNCBr), 3.48 (m, 1 H, CHN), 3.33 (dd, J = 7.8, 19.0 Hz, 1 H, CH_aH$_b$CO), 3.03 (dd, J = 3.0, 19.0 Hz, 1 H, CH$_a$$H_b$CO), 2.72 (dm, J = 13.7 Hz, 1 H, CH_aH$_{b\text{ allyl}}$), 2.45–2.35 (m, 2 H, CH$_a$$H_{b\text{ allyl}}$, C$H_aH_{b\text{ cycle}}$), 2.32–2.21 (m, 1 H, CH$_a$$H_{b\text{ cycle}}$), 2.25 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 204.33 (C=O), 132.74, 128.98, 119.65, 116.71, 51.87, 51.78, 47.25, 43.54, 36.18, 30.38, 29.55 ppm. MS (70 eV, EI): m/z (%) = 258/260 (9) [M – Cl]$^+$, 216/218 (11), 198/200 (7), 158/160 (100), 120 (12), 93 (7), 78 (12), 65(6), 51 (6), 43 (6). $C_{11}H_{17}BrClNO_2$ (294.6): calcd. C 44.84, H 5.82, N 4.75; found C 44.83, H 5.86, N 4.73.

(2*R,6*S**)-6-Allyl-5-bromo-2-(2-oxopropyl)-1,2,3,6-tetrahydropyridinium Hydrochloride (8b):** Yield: 0.15 g (92%) as cream-colored crystals, m.p. 118.5–119.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.66 and 9.12 (br. s., 1.4 H in total, NH$_2^+$), 6.23 (s, 1 H, CH=$_{\text{cycle}}$), 5.95–5.84 (m, 1 H, CH=$_{\text{allyl}}$), 5.43 (d, J = 16.8 Hz, 1 H, CH_aH$_b$=$_{\text{allyl}}$), 5.29 (d, J = 10.0 Hz, 1 H, CH$_a$$H_b$=$_{\text{allyl}}$), 4.08 (br. s., 1 H, CHN$_{\text{allyl}}$), 3.89 (m, 1 H, CHNCH$_2$CO), 3.47 (dd, J = 4.6, 18.5, Hz, 1 H, CH_aH$_b$CO), 3.01–2.90 (m, 2 H, CH_aH$_b$CO and CH_aH$_{b\text{ allyl}}$), 2.77 (m, 1 H, CH$_a$$H_{b\text{ allyl}}$), 2.49 (m, 2 H, CH$_{2\text{ cycle}}$), 2.18 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.04 (C=O), 130.88, 128.25, 121.94, 115.91, 56.50, 45.23, 44.58, 34.96, 30.37, 29.67 ppm. $C_{11}H_{17}BrClNO_2$ (294.6): calcd. C 44.84, H 5.82, N 4.75; found C 44.81, H 5.82, N 4.68.

X-ray Diffraction of 2b: $C_{13}H_{20}BrNO_2$, M_r = 302.21, orthorhombic, space group $Pbca$, T = 100.0(2) K; a = 17.608(2), b = 7.2047(9), c = 21.431(2) Å, V = 2718.7(5) Å^3, Z = 8, $d_{\text{calcd.}}$ = 1.477 g cm^{-3}, F(000) = 1248, μ = 3.015 mm^{-1}. Data were collected with a Bruker three-circle diffractometer equipped with a SMART APEX-II CCD area detector using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å, ϕ- and ω-scan mode, 2θ = 56°) and corrected for Lorentz, polarization and absorption effects.[16] The structure was solved by direct methods and refined by full-matrix least-squares refinement on F^2 with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were generated geometrically and included in the refinement with fixed positions and thermal parameters. The final R factors were R_1 = 0.0314 for 2594 reflections with $I \geq 2\sigma(I)$ and wR_2 = 0.0769 for all 3233 (R_{int} = 0.060) independent reflections. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.536 and –0.566 e Å^{-3}, respectively. All calculations were carried out using the SHELXTL (PC Version 6.12) program.[17] CCDC-628827 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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