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Synthesis of bicyclic carbamates as precursors of Sedum alkaloid derivatives

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Abstract—Synthesis of a *N*-Boc-protected piperidin-2-yl phosphine oxide starting from piperidine in three steps, followed by olefination using a variety of α,β-unsaturated aldehydes resulted in *tert*-butyl 2-(2′-alkenylidene)piperidine-1-carboxylates in high yields. A novel type of intramolecular cyclization of these enamides furnished a new family of 3-alkyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-ones as useful substrates for further elaboration. Subsequent reduction of these unsaturated bicyclic carbamates using $NaCNBH_3$ or $NaBH_4$ afforded the corresponding 3-alkylhexahydropyrido[1,2-*c*][1,3]oxazin-1-ones in a highly stereoselective way. Reductive ring opening of two representatives furnished the corresponding Sedum alkaloid derivatives in good yields.

1. Introduction

Biologically active alkaloids bearing a substituted piperidine ring have been the objective of considerable synthetic efforts.[1,2] Among others, the Sedum alkaloids constitute an extensive family of 2-substituted and 2,6-disubstituted piperidines, many of which feature the 1,3-aminoalcohol moiety, for example, allosedridine (**1** [2*R*-(2′*S*)], $R^1=R^2=R^3=H$), sedridine (**1** [2*S*-(2′*S*)], $R^1=R^2=R^3=H$) and halosaline (**1**, $R^1=Et$, $R^2=R^3=H$) (Fig. 1).[2–5] Although the interest in the synthesis of these alkaloids has been ongoing for nearly half a century, the synthetic derivatives have mainly been used as a testing ground for the control of the stereochemistry of the 1,3-aminoalcohol system.[2] Only recently the memory-enhancing properties and the potential use as anti-Alzheimer agents have put the Sedum alkaloids in a new perspective,[6] hence the renewed interest in the preparation of these compounds and related structures with potential physiological activities. A large variety of syntheses towards Sedum alkaloids are known in the literature. Most of these strategies are based on the use of a preformed nitrogen heterocycle onto which a side-chain is appended. This group can be subdivided into those involving a pyridine and those involving a piperidine moiety.[2] Sedum alkaloids have also been synthesized by cycloaddition reactions with nitrones and by other techniques for construction of the heterocycle, such as intramolecular Michael additions, metathesis reactions, condensations (e.g., between an imine and an ester or between an aminoalcohol and an aldehyde) and alkylations with haloalkanes (e.g., using an α-cyanopiperidine) or haloalkenes and epoxides (with e.g., dithiane).[2]

A key intermediate in many synthetic pathways towards Sedum alkaloids is the bicyclic carbamate **2**, since cleavage of this moiety affords the desired 1,3-aminoalcohol unit and liberates the piperidine ring (Fig. 1).[2] In this report a novel synthesis of unsaturated bicyclic carbamates as precursors of Sedum alkaloid derivatives is described, based on the intramolecular nucleophilic attack of a *N*-Boc group onto an in situ formed iminium species. According to the retrosynthetic pathway in Figure 1, bicyclic carbamates **2** can be prepared by cyclization of enamides **3**, which can be useful starting materials for the synthesis of piperideine alkaloids **4**, for example, nigrifactin ($R^1=(2E)$-butenylidene, $R^2=H$) or 2-(2′-propenyl)-1-piperideine ($R^1=R^2=H$), an alkaloid from the leaves of *Punica granatum*.[7–9]

2. Results and discussion

The synthetic pathway leading to 2-(2′-alkenylidene)piperidine-1-carboxylates **3a–f** and **9** is depicted in Scheme 1. The phosphorylated carbamate **5** was readily prepared in three steps via the formation of the 2,3,4,5-tetrahydropyridine

Keywords: Enamide; Bicyclic carbamate; Stereoselectivity; Sedum alkaloid.

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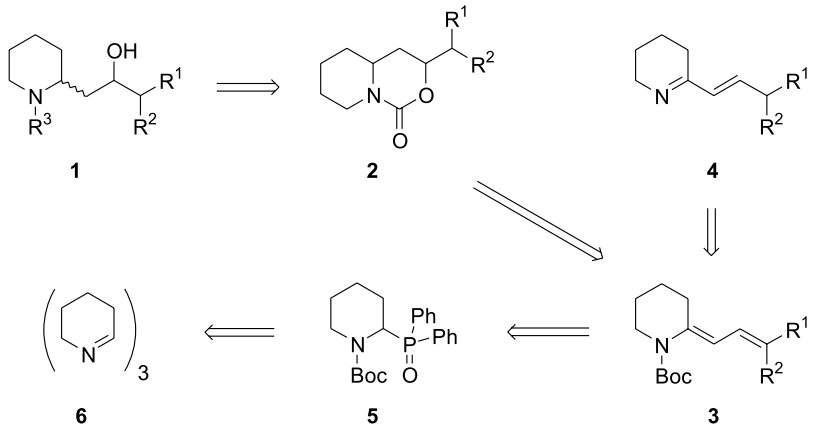
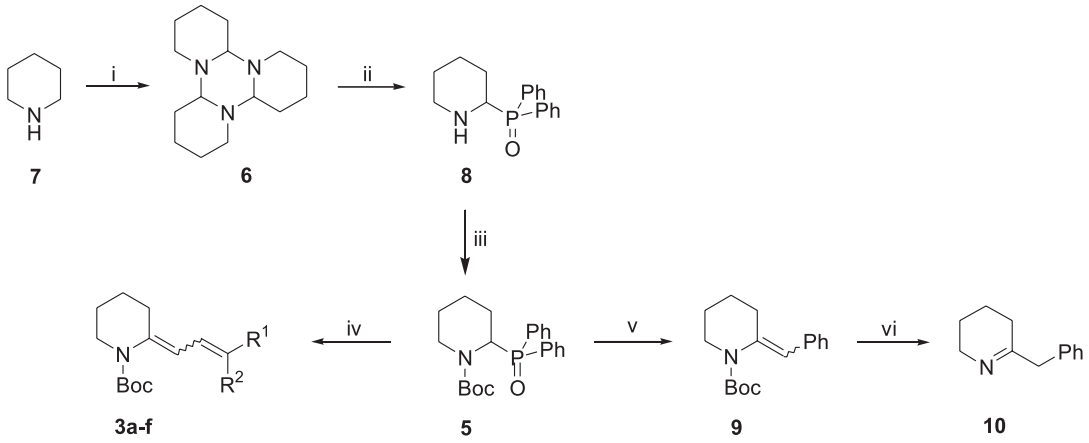


Figure 1.

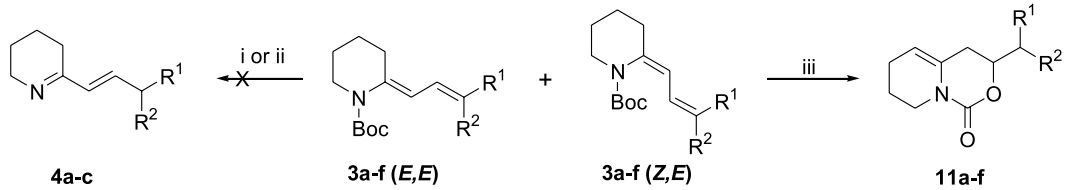


Scheme 1. (i) *t*-BuOCl, Et_2O, 0 °C, then 2 N NaOMe, MeOH, 45 min reflux; 65%; (ii) 1 equiv $Ph_2P(O)H$, toluene, 3 h reflux; 92%; (iii) 1.2 equiv Boc_2O, 1 equiv triethylamine, 5 mol% DMAP, THF, 40 °C, 6 h; 78%; (iv) 1.25 equiv BuLi, THF, −78 °C, 1 equiv of $R^1R^2C{=}CH{-}CHO$, with **a**: $R^1{=}R^2{=}H$; **b**: $R^1{=}Me$, $R^2{=}H$; **c**: $R^1{=}Ph$, $R^2{=}H$; **d**: $R^1{=}Me$, $R^2{=}Me$; **e**: $R^1{=}i$-Pr, $R^2{=}H$; **f**: $R^1{=}4\text{-}MeOC_6H_4$, $R^2{=}H$; **5**: 33–68% after chromatography; (v) 1.25 equiv BuLi, 1 equiv PhCHO, THF, −78 °C to rt, 2 h, 90%; (vi) 19 equiv TFA, CH_2Cl_2, 0 °C, 30 min, 81%.

trimer **6** from piperidine using *t*-BuOCl and NaOMe,[10] followed by phosphorylation with 1 equiv of diphenylphosphine oxide in toluene and protection of the resulting amine **8** with 1.2 equiv of di-*tert*-butyl dicarbonate, 1 equiv of triethylamine and 5 mol% DMAP in THF, furnishing the Boc-protected piperidin-2-yl phosphine oxide **5** in 78% yield.[10–12] The modified Horner reaction between this phosphorylated carbamate **5** and 1 equiv of various α,β-unsaturated aldehydes or benzaldehyde using 1.25 equiv of BuLi in THF at −78 °C resulted in new enamides **3a–f** and **9** in good to excellent yields after 2 h at room temperature (Scheme 1).[12,13]

Deprotection of enamide **9** using an excess of TFA in CH_2Cl_2 afforded 2-benzylpiperideine **10** in 81% yield.[14,15] Consequently, this method seemed suitable for the preparation of piperideine alkaloids, for example, 2-(2′-propenyl)-1-piperideine ($R^1{=}R^2{=}H$), an alkaloid in the pomegranate (see **4**, Fig. 1).[7] Although Boc-deprotection of enamides **3** bearing a diene function was attempted using an excess of TFA in CH_2Cl_2 or 1.5 equiv of trimethylsilyl iodide in CH_3CN, only a complex mixture of unknown compounds was obtained, even though the conditions applied were very mild (−10 to 0 °C, workup at 0 °C) (Scheme 2).

Further investigation of the literature lead to the application of other methods for the removal of a *N*-Boc group, for example, the use of Me_3SiI and phenol in CH_2Cl_2. To the



Scheme 2. (i) TFA, CH_2Cl_2, 0 °C to rt, 30 min; (ii) 1.5 equiv TMS-I, 1.5 equiv H_2O, MeCN; (iii) 1.5 equiv TMS-I, 1.5 equiv phenol, CH_2Cl_2, rt, 30 min; **a**: $R^1{=}R^2{=}H$; **b**: $R^1{=}Me$, $R^2{=}H$; **c**: $R^1{=}Ph$, $R^2{=}H$; **d**: $R^1{=}Me$, $R^2{=}Me$; **e**: $R^1{=}i$-Pr, $R^2{=}H$; **f**: $R^1{=}4\text{-}MeOC_6H_4$, $R^2{=}H$; 41–70% after chromatography.

enamides **3a–f** was added a mixture of 1.5 equiv of trimethylsilyl iodide and 1.5 equiv of phenol in CH_2Cl_2, resulting in the unsaturated bicyclic carbamates **11a–f** in good yields after 30 min at room temperature (Scheme 2), which were subsequently purified by means of column chromatography.

The reactivity of the *N*-Boc protecting group has been well documented in the literature.[16] An important feature of the *N*-Boc group is the possibility to react intramolecularly as an electrophile or as a nucleophile, furnishing a cyclic carbamate. The intramolecular nucleophilic reactivity generally results from the presence of an electrophilic carbon atom due to a carbenium ion, a halonium ion or a good leaving group attached to the electrophilic centre. This centre is then attacked by the substantial negative charge on the carbonyl oxygen of the Boc-group.[17] Indeed, the combination of trimethylsilyl iodide and phenol leads to the formation of trimethylsilyl phenoxide with the liberation of hydrogen iodide.[18] In this medium, the Boc-group of compound **3** is cleaved upon expulsion of isobutene, and the iminium species **13**, in situ formed due to the presence of hydrogen iodide, undergoes intramolecular trapping by the oxygen anion furnishing carbamate **14**. It should be noted that the double bond in compound **14** shifts from its initial position in the carbamate ring to the piperidine ring upon isomerization in the acidic medium, resulting in the isolated carbamates **11** (Scheme 3).

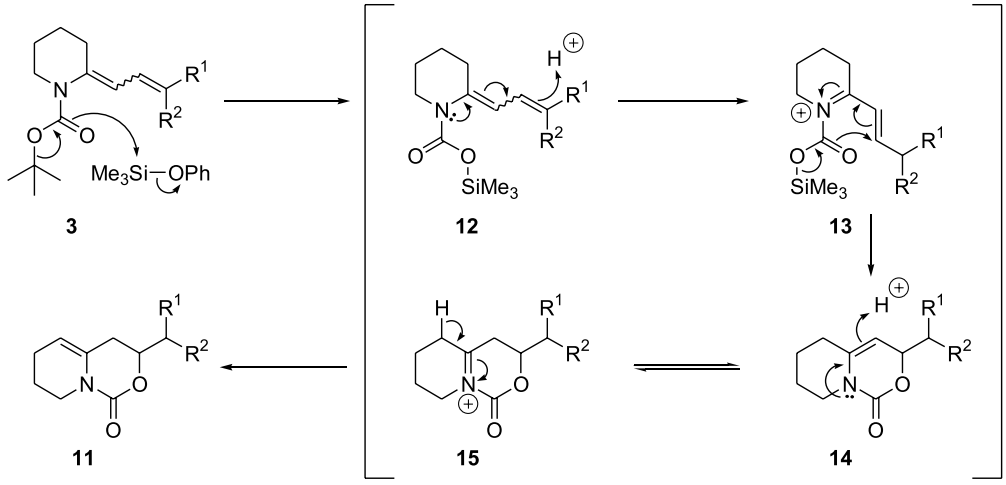
When the unsaturated bicyclic carbamates **11a** and **11b** were reduced with either 3 equiv of $NaCNBH_3$ in MeOH or with 4 equiv of $NaBH_4$, both in glacial AcOH, a mixture of diastereomers of the saturated carbamates **2** [**2a** (*cis*/*trans*=86/14) and **2b** (*cis*/*trans*=88/12)] was obtained (Scheme 4). NOESY experiments revealed that the major component was the *cis*-isomer. Reduction of carbamate **11c** with 4 equiv of $NaBH_4$ in glacial AcOH resulted selectively in the *cis* compound **2c**. Reduction of the saturated bicyclic carbamates **2a** and **2b** with 2 equiv of $LiAlH_4$ in THF upon reflux for 1 h, followed by purification on silica gel, gave rise to the known racemic Sedum alkaloids ($2R^*,2'S^*$)-*N*-methylallosedridine **1a** and ($2R^*,2'S^*$)-1-(1-methylpiperidin-2-yl)butan-2-ol **1b**.[19–21]

3. Conclusions

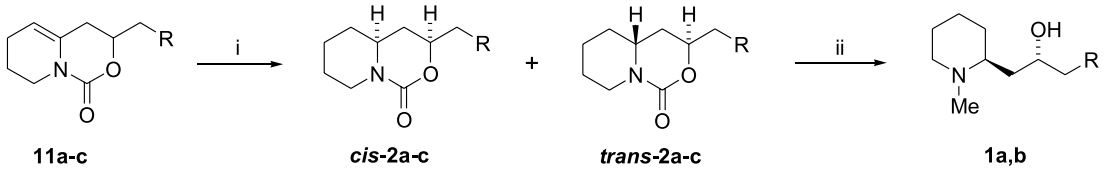
A new, efficient and straightforward synthesis of 3-alkyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-ones has been developed, based on the synthesis of an *N*-Boc-protected piperidin-2-yl phosphine oxide in three steps from piperidine, followed by olefination with a variety of α,β-unsaturated aldehydes and finally a new type of intramolecular cyclisation of the *N*-Boc group onto an in situ formed iminium species upon treatment with trimethylsilyl iodide and phenol in dichloromethane. Subsequent reduction of the resulting unsaturated bicyclic carbamates with $NaCNBH_3$ or $NaBH_4$ in glacial AcOH and reductive ring opening furnished the corresponding Sedum alkaloid derivatives in good yields.

4. Experimental

^{1}H NMR spectra were recorded at 270 MHz (JEOL JNM-EX 270) or at 300 MHz (JEOL Eclipse+ 300) or at 400 MHz (Bruker Avance DRX 400 spectrometer), with $CDCl_3$ as solvent and TMS as internal standard. ^{13}C NMR



Scheme 3.



Scheme 4. (i) 3 equiv $NaCNBH_3$, MeOH, reflux, 72 h or 4 equiv $NaBH_4$, AcOH, rt, 5 h; **a**: R=H, *cis*/*trans*=86/14; **b**: R=Me, *cis*/*trans*=88/12; **c**: R=Ph, *cis*/*trans*=100/0 (4 equiv $NaBH_4$, AcOH, rt, 3 h); 80%; (ii) $LiAlH_4$, THF or Et_2O, reflux; 1 h; 65–66%, then flash chromatography.

spectra were recorded at 68 MHz (JEOL JNM-EX 270) or at 75 MHz (JEOL ECLIPSE+ 300) in $CDCl_3$. IR spectra were measured with a Perkin–Elmer Spectrum One FT-IR. Mass spectra were recorded with an Agilent 1100 (series: MS, detector: VL, 70 eV, ES 4000 V) or with a (Varian MAT 112 (70 eV) mass spectrometer using GC–MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas). Microanalyses were determined on a Perkin–Elmer 2400 elemental analyser. Melting points were performed on a Kofler apparatus and are uncorrected. Et_2O and THF were dried by distillation over sodium benzophenone ketyl. Ethanol was used as received from the supplier. 2,3,4,5-Tetrahydropyridine trimer **6**, 2-(diphenylphosphinoyl)piperidine **8** and its Boc carbamate derivative **5** were prepared according to literature methods.[10–12]

4.1. General method for the synthesis of *tert*-butyl 2-(2′-alkenylidene)piperidine-1-carboxylates 3a–f and 9

As a representative example, the synthesis of *tert*-butyl 2-(2′-propenylidene)piperidine-1-carboxylate **3a** is described. To a solution of phosphorylated piperidine derivative **5** (0.39 g, 1 mmol) in THF (5 mL), *n*-BuLi (0.5 mL, 1.25 mmol, 2.5 M in *n*-hexane) was added dropwise at −78 °C under a N_2 atmosphere. The orange mixture was stirred for 20 min at −78 °C, followed by the addition of a solution of acrolein (0.056 g, 1 mmol) in THF (2 mL) via a syringe. After a further stirring period of 20 min at −78 °C, the reaction mixture was allowed to warm up to room temperature during stirring for 2 h. Addition of water (10 mL), extraction with Et_2O (3×10 mL), drying ($MgSO_4$), filtration and evaporation in vacuo afforded the crude product **3a**, which was purified by column chromatography with petrol ether/ethyl acetate (90/10), yielding pure **3a** (0.105 g, 47%). All NMR data of compounds **3a–f** are derived from mixtures of the *E* and *Z*-isomers at position 2.

4.1.1. *tert*-Butyl 2-[(2′*E*)-2′-propenylidene]piperidine-1-carboxylate 3a. Mixture of *E* and *Z*-isomers, ratio *E*/*Z*=67/33. Flash chromatography (petrol ether/EtOAc 9/1, R_f=0.58). Yield: 47%, pale-yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1712. *Major isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.26–1.69 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.45 (9H, s, *t*Bu); 2.12–2.21 (2H, m, $CH_2(CH_2)_3N$); 3.52 (1H, t, J=5.5 Hz, (HC*H*)N); 4.99 (1H, d, J=10.6 Hz, CH=(*H*CH)); 5.14 (1H, d, J=17.0 Hz, CH=(HC*H*)); 5.77 (1H, d, J=10.6 Hz, NC=CH); and 6.32 (1H, dt, J=10.6, 17.0 Hz, NC=CHC*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.4 and 26.6 ($NCH_2(CH_2)_2$); 28.2 ($(CH_3)_3C$); 33.0 ($N(CH_2)_3CH_2$); 46.5 (CH_2N); 79.7 ($(CH_3)_3C$); 115.3 (CH=CH_2); 122.0 and 132.6 (NC=*CH*C*H*); 139.0 (N*C*=CH) and 153.1 (C=O). MS (70 eV) *m*/*z* (%): 223 (M^+, 14); 167 (100); 152 (29); 150 (24); 123 (51); 122 (65); 108 (41); 95 (12); 94 (28); 80 (20); 67 (11); 57 (69); 55 (13); and 41 (41). *Minor isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.26–1.69 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.46 (9H, s, *t*Bu); 2.08–2.18 (2H, m, $CH_2(CH_2)_3N$); 3.35–3.38 (1H, m, (HC*H*)N); 5.07–5.21 (2H, m, CH=CH_2); 5.95 (1H, d, J=10.6 Hz, NC=CH); and 6.55 (1H, dt, J=10.6, 10.8 Hz, NC=CHC*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.3 and 26.9 ($NCH_2(CH_2)_2$); 28.3 ($(CH_3)_3C$); 33.0 ($N(CH_2)_3CH_2$); 46.3 (CH_2N); not recognizable ($(CH_3)_3C$); 116.2 (CH=CH_2); 124.1 and 131.8 (NC=*CH*C*H*); 139.1 (N*C*=CH); and 153.1 (C=O). MS (70 eV) *m*/*z* (%): 223 (M^+, 12); 167 (90); 152 (25); 150 (11); 123 (42); 122 (69); 108 (39); 95 (12); 94 (22); 80 (17); 67 (9); 57 (100); 55 (13); and 41 (49). Anal. calcd for $C_{13}H_{21}NO_2$ (223.31): C, 69.92; H, 9.48; N, 6.27; found C, 69.81; H, 9.56; N, 6.19.

4.1.2. *tert*-Butyl 2-[(2′*E*)-2′-butenylidene]piperidine-1-carboxylate 3b. Mixture of *E* and *Z* isomers, ratio *E*/*Z*=86/14. Flash chromatography (petrol ether/EtOAc 9/1, R_f=0.70). Yield: 54%, yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1694. *Major isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.26–1.79 (8H, m, CH_3, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.45 (9H, s, *t*Bu); 2.14 (2H, br s, $CH_2(CH_2)_3N$); 3.35–3.38 (1H, m, (HC*H*)N); 5.59–5.70 (2H, m, H_a and H_c); and 5.96–6.06 (1H, m, H_b). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.3 (CH_3); 25.6 and 26.8 ($NCH_2(CH_2)_2$); 28.3 ($(CH_3)_3C$); 33.1 ($N(CH_2)_3CH_2$); 46.7 (CH_2N); 79.5 ($(CH_3)_3C$); 123.2, 126.5 and 141.4 (CH_a, CH_b and CH_c); 136.9 (N*C*=CH); and 153.6 (C=O). MS (70 eV, direct inlet) *m*/*z* (%): 237 (M^+, 14); 181 (100); 164 (21); 137 (27); 136 (78); 122 (30); 108 (28); 94 (20); 57 (55); and 41 (17). *Minor isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.26–1.79 (8H, m, CH_3, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.45 (9H, s, *t*Bu); 2.28–2.30 (2H, m, $CH_2(CH_2)_3N$); 3.48–3.52 (1H, m, (HC*H*)N); 5.39–5.55 (1H, m, H_c); 5.88 (1H, d, J=10.9 Hz, H_a); and 6.17–6.29 (1H, m, H_b). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.42 (CH_3); 25.8 and 27.0 ($NCH_2(CH_2)_2$); 28.5 ($(CH_3)_3C$); 33.7 ($N(CH_2)_3CH_2$); 46.3 (CH_2N); 79.5 ($(CH_3)_3C$); not recognizable (CH_a, CH_b, CH_c); 136.3 (N*C*=CH); and 153.6 (C=O). MS (70 eV) *m*/*z* (%): 237 (M^+, 13); 181 (100); 164 (7); 137 (29); 136 (87); 122 (36); 108 (29); 94 (21); 57 (71); and 41 (23). Anal. calcd for $C_{14}H_{23}NO_2$ (237.41): C, 70.85; H, 9.77; N, 5.90; found C, 70.98; H, 9.86; N, 5.83.

4.1.3. *tert*-Butyl 2-[(2′*E*)-3′-phenyl-2′-propenylidene]piperidine-1-carboxylate 3c. Mixture of *E* and *Z* isomers, ratio *E*/*Z*=76/24. Flash chromatography (petrol ether/EtOAc 9/1, R_f=0.42). Yield: 68%, white crystals, mp: 106–107 °C. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1691. *Major isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.28–1.73 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.47 (9H, s, *t*Bu); 2.20–2.25 (1H, m, (*H*CH)$(CH_2)_3N$); 2.44 (1H, t, J=5.9 Hz, (HC*H*)$(CH_2)_3N$); 3.55 (1H, t, J=5.5 Hz, (HC*H*)N); 5.92 and 6.47 (2×1H, 2×d, J=11.2, 15.5 Hz, H_a and H_c); 6.77 (1H, dd, J=11.2, 15.5 Hz, H_b); and 7.19–7.41 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.4 and 25.5 ($NCH_2(CH_2)_2$); 28.3 ($(CH_3)_3C$); 33.4 ($N(CH_2)_3CH_2$); 46.6 (CH_2N); 79.9 ($(CH_3)_3C$); 121.7, 127.3 and 130.6 (CH_a, CH_b and CH_c); 124.7 (HC_{para}); 126.3 and 128.6 (2×HC_{ortho} and 2×HC_{meta}); 137.64 (N*C*=CH); 139.6 ($C_{arom,quat}$); and 153.6 (C=O). MS (70 eV, direct inlet) *m*/*z* (%): no M^+; 243 (M^+-isobutene, 100); 199 (63); 156 (15); 115 (17); 97 (11); 57 (31); and 41 (15). *Minor isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.28–1.73 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.46 (9H, s, *t*Bu); 2.20–2.46 (2H, m, $CH_2(CH_2)_3N$); 3.34–3.40 (1H, m, (HC*H*)N); 6.12 and 6.51 (2×1H, 2×d, J=11.2, 15.5 Hz, H_a and H_c); 6.98 (1H, dd, J=11.2, 15.5 Hz, H_b); and 7.19–7.41 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): recognizable signal: δ 28.5 ($(CH_3)_3C$). Anal. calcd for $C_{19}H_{25}NO_2$ (299.41): C, 76.22; H, 8.42; N, 4.68; found C, 76.05; H, 8.25; N, 4.80.

4.1.4. *tert*-Butyl 2-[(2′*E*)-3′-methyl-2′-butenylidene] piperidine-1-carboxylate 3d. Mixture of *E* and *Z* isomers, ratio *E*/*Z*=86/14. Flash chromatography (petrol ether/EtOAc 9/1, R_f=0.67). Yield: 60%, yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1677. *Major isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.35–1.93 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.45 (9H, s, *t*Bu); 1.74 and 1.78 (6H, 2×s, 2×CH_3); 2.12–2.19 (2H, m, $CH_2(CH_2)_3N$); 3.51 (1H, t, *J*=5.3 Hz, (HC*H*)N); and 5.75 and 5.89 (2×1H, 2×d, *J*=10.9 Hz, H_a and H_b). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.6 and 26.9 ($NCH_2(CH_2)_2$); 26.1 (2×CH_3); 28.3 ($(CH_3)_3C$); 33.4 ($N(CH_2)_3CH_2$); 46.7 (CH_2N); 79.3 ($(CH_3)_3C$); 119.8 and 120.9 (CH_a and CH_b); 136.4, 142.6 and 154.2 (3×C_{quat}). MS (70 eV) *m*/*z* (%): 251 (M^+, 12); 195 (100); 178 (12); 151 (17); 150 (29); 136 (60); 122 (8); 108 (10); 57 (36); and 41 (17). *Minor isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.35–1.93 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.43 (9H, s, *t*Bu); 1.81 and 1.90 (2×CH_3); 2.12–2.19 (2H, m, $CH_2(CH_2)_3N$); 3.35 (1H, t, *J*=5.3 Hz, (HC*H*)N); and 5.96 and 6.10 (2×1H, 2×d, *J*=11.1 Hz, H_a and H_b). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.8 and 27.8 ($NCH_2(CH_2)_2$); 25.6 (2×CH_3); 28.5 ($(CH_3)_3C$); not recognizable ($N(CH_2)_3CH_2$ and CH_2N); and 79.4 ($(CH_3)_3C$); not recognizable (CH_a, CH_b and 3×C_{quat}). MS (70 eV) *m*/*z* (%): no M^+; 181 (100); 164 (17); 136 (73); 122 (29); 108 (28); 94 (22); 57 (77); and 41 (35). Anal. calcd for $C_{15}H_{25}NO_2$ (251.36): C, 71.67; H, 10.02; N, 5.57; found C, 71.81; H, 9.87; N, 5.66.

4.1.5. *tert*-Butyl 2-[(2′*E*)-4′-methyl-2′-pentenylidene] piperidine-1-carboxylate 3e. Mixture of *E* and *Z* isomers, ratio *E*/*Z*=92/8. Flash chromatography (petrol ether/EtOAc 9/1, R_f=0.65). Yield: 53%, yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1692. *Major isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.00 (6H, d, *J*=6.9 Hz, $CH(CH_3)_2$); 1.42–1.68 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.42 (9H, s, *t*Bu); 2.02–2.24 (2H, m, $CH_2(CH_2)_3N$); 2.27–2.39 (1H, m, $CH(CH_3)_2$); 3.36 (1H, t, *J*=5.3 Hz, (HC*H*)N); 5.55–5.71 (2H, m, H_a and H_c); and 5.87–6.01 (1H, m, H_b). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.4 ($CH(CH_3)_2$); 25.6 and 26.7 ($NCH_2(CH_2)_2$); 28.3 ($(CH_3)_3C$); 31.4 ($CH(CH_3)_2$); 33.1 ($N(CH_2)_3CH_2$); 46.1 (CH_2N); 79.4 ($(CH_3)_3C$); 121.7 and 140.3 (CH_a and CH_c); 123.1 (CH_b); 136.4 (N*C*=CH); and 153.6 (C=O). MS (70 eV) *m*/*z* (%): 265 (M^+, 16); 209 (93); 194 (51); 164 (34); 150 (100); 136 (20); 122 (27); 97 (22); 57 (51); and 41 (15). *Minor isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.01 (6H, d, *J*=6.6 Hz, $CH(CH_3)_2$); 1.42–1.68 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.46 (9H, s, *t*Bu); 2.02–2.24 (2H, m, $CH_2(CH_2)_3N$); 2.27–2.39 (1H, m, $CH(CH_3)_2$); 3.50 (1H, t, *J*=5.4 Hz, (HC*H*)N); 5.40–5.71 (2H, m, H_a and H_c); and 6.11–6.17 (1H, m, H_b). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.4 ($CH(CH_3)_2$); 25.8 and 27.0 ($NCH_2(CH_2)_2$); 28.4 ($(CH_3)_3C$); 31.5 ($CH(CH_3)_2$); not recognizable ($N(CH_2)_3CH_2$ and CH_2N); 79.5 ($(CH_3)_3C$); 122.1 and 141.3 (CH_a and CH_c); 124.0 (CH_b); 136.6 (N*C*=CH); and 153.6 (C=O). MS (70 eV) *m*/*z* (%): 265 (M^+, 12); 209 (82); 194 (41); 164 (40); 150 (100); 136 (11); 122 (54); 97 (24); 57 (53); and 41 (21). Anal. calcd for $C_{16}H_{27}NO_2$ (265.39): C, 72.41; H, 10.25; N, 5.28; found C, 72.29; H, 10.20; N, 5.40.

4.1.6. *tert*-Butyl (2*E*)-2-[(2′*E*)-3′-(4-methoxyphenyl)-2′-propenylidene)]piperidine-1-carboxylate 3f. Flash chromatography (petrol ether/EtOAc 9/1, R_f=0.40). Yield: 33%, white crystals, mp 138–139 °C. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1677. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22–1.73 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.38 (9H, s, *t*Bu); 2.11–2.32 (2H, m, $CH_2(CH_2)_3N$); 2.77–2.79 (1H, m, (HC*H*)N); 5.89 and 6.42 (2×1H, 2×d, *J*=10.6, 15.7 Hz, H_a and H_c); 6.63 (1H, dd, *J*=10.6, 15.7 Hz, H_b); 6.83 (2H, d, *J*=8.7 Hz, 2×MeOCH_{ortho}); and 7.32 (2H, d, *J*=8.7 Hz, 2×MeOCH_{meta}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.6 and 26.8 ($NCH_2(CH_2)_2$); 28.3 ($(CH_3)_3C$); 33.3 ($N(CH_2)_3CH_2$); 46.3 (CH_2N); 55.3 (CH_3O); 79.7 ($(CH_3)_3C$); 114.1 (2×MeOC$_{ortho}$); 121.8 (CH_a or CH_c); 122.7 (CH_b); 128.6 (2×MeOC$_{meta}$); 128.5, 130.1, 138.6 ($C_{arom,quat}$; N*C*=CH and CH_a or CH_c); 153.9 (C=O); and 159.1 (COMe). MS (70 eV) *m*/*z* (%): 329 (M^+, 23); 273 (66); 256 (10); 229 (88); 228 (100); 214 (27); 186 (12); 97 (39); and 57 (22). Anal. calcd for $C_{20}H_{27}NO_2$ (329.43): C, 72.92; H, 8.26; N, 4.25; found C, 72.81; H, 8.16; N, 4.33.

4.1.7. *tert*-Butyl 2-benzylidenepiperidine-1-carboxylate 9. Mixture of *E* and *Z* isomers, ratio *E*/*Z*=77/23. Flash chromatography (petrol ether/EtOAc 9/1, R_f=0.65). Yield: 90%, white crystals, mp 86–88 °C. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1652. *Major isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.47 (9H, s, *t*Bu); 1.54–1.67 (4H, m, $(CH_2)_2CH_2N$); 2.39–2.43 (2H, m, $CH_2(CH_2)_3N$); 3.57–3.62 (2H, m, CH_2N); 6.39 (1H, s, NC=CH); and 7.15–7.36 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): 25.6 and 27.3 ($NCH_2(CH_2)_2$); 28.3 ($(CH_3)_3C$); 34.1 ($N(CH_2)_3CH_2$); 46.6 (CH_2N); 79.6 ($(CH_3)_3C$); 124.2 (HC$_{para}$); 126.4 (NC=*C*H); 128.1 and 128.7 (2×HC$_{ortho}$ and 2×HC$_{meta}$); 136.7 (N*C*=CH); 139.3 ($C_{arom,quat}$); and 154.2 (C=O). MS (70 eV, direct inlet) *m*/*z* (%): 274 (M^++1, 8); 273 (M^+, 16); 217 (80); 173 (37); and 57 (100). *Minor isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.47 (9H, s, *t*Bu); 1.54–1.67 (4H, m, $(CH_2)_2CH_2N$); 2.29–2.31 (2H, m, $CH_2(CH_2)_3N$); 3.35–3.38 (2H, m, CH_2N); 6.05 (1H, s, NC=CH); and 7.15–7.36 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): 25.3 and 26.9 ($NCH_2(CH_2)_2$); 27.7 ($(CH_3)_3C$); 34.1 ($N(CH_2)_3CH_2$); 45.8 (CH_2N); 79.4 ($(CH_3)_3C$); 120.5 and 126.5 (HC$_{para}$ and NC=*C*H); 127.7 and 128.3 (2×HC$_{ortho}$ and 2×HC$_{meta}$); 136.8 (N*C*=CH); 138.4 ($C_{arom,quat}$); and 152.8 (C=O). Anal. calcd for $C_{17}H_{23}NO_2$ (273.37): C, 74.69; H, 8.48; N, 5.12; found C, 74.51; H, 8.61; N, 5.29.

4.1.8. 6-Benzyl-2,3,4,5-tetrahydropyridine 10. To a solution of 0.19 g (0.7 mmol) of *tert*-butyl 2-benzylidenepiperidine-1-carboxylate **9** in dry CH_2Cl_2 (8 mL), TFA (1 mL) was added in one portion at 0 °C. The mixture was stirred at 0 °C for 30 min (the reaction was monitored by means of TLC) and subsequently the solution was poured onto ice-cold water (20 mL), basified with 10% NaOH solution and extracted with Et_2O (3×25 mL). The combined organic phases were dried ($MgSO_4$) and evaporated, and the crude product obtained was purified by flash chromatography on a silica gel column with EtOAc/Et_3N (9/1), resulting in 0.098 g (81%) of the oily cyclic imine **10**. The spectroscopic data on compound **10** corresponded to those reported in the literature.[15]

IR (NaCl, cm^{-1}): $\nu_{C=O}$=3368; 2928; 1660; 1483; 1110; and 695. ^{1}H NMR ($CDCl_3$): δ 1.50–1.62 (m, 4H, 2×CH_2); 2.02–2.07 (m, 2H, CH_2); 3.47 (s, 2H, CH_2); 3.60–3.64 (m, 2H, CH_2); and 7.19–7.23 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ

19.4; 21.6; 28.0; 48.1; 49.3; 126.3; 128.3; 128.9; 137.7; and 169.7.

4.2. Synthesis of 3-alkyl-4,6,7,8-tetrahydro-3*H*-pyrido [1,2-*c*][1,3]oxazin-1-ones 11a–f. As a representative example, the synthesis of 3-methyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one **11a** is described. To a solution of Me_3SiI (3.00 g, 15 mmol) and phenol (1.41 g, 15 mmol) in CH_2Cl_2 (40 mL), *tert*-butyl (2*E*)-2-(2-propenylidene)piperidine-1-carboxylate **3a** (2.23 g, 10 mmol) in CH_2Cl_2 (10 mL) was added at room temperature, and the resulting mixture was stirred for 30 min. The reaction mixture was then poured into 4 N NaOH solution (20 mL), extracted with CH_2Cl_2 (3×20 mL), dried ($MgSO_4$), filtered and evaporated in vacuo, furnishing crude 3-methyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one **11a**, which was purified by column chromatography with petrol ether/EtOAc (3/2), yielding pure **11a** (0.69 g, 41%).

4.2.1. 3-Methyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one 11a. Flash chromatography (petrol ether/EtOAc 3/2, R_f=0.25). Yield: 41%, pale-yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1666. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (3H, d, J=6.1 Hz, CH_3); 1.80–1.98 (2H, m, NCH_2CH_2); 2.02–2.08 (2H, m, $N(CH_2)_2CH_2$); 2.29–2.51 (2H, m, $NCCH_2$); 3.52 (1H, ddd, J=4.8, 8.1, 12.9 Hz, (*H*CH)N); 3.84–3.93 (1H, m, (HC*H*)N); 4.34–4.44 (1H, m, CHO); and 4.70 (1H, br s, NC=CH). ^{13}C NMR (75 MHz, $CDCl_3$): 20.42 (CH_3); 21.8 ($NCH_2(CH_2)_2$); 34.9 ($NCCH_2$); 42.9 (CH_2N); 72.4 (OCH); 103.7 (NC=*C*H); 130.4 (N*C*=CH); and 151.2 (C=O). MS (70 eV) *m*/*z* (%): 167 (M^+, 70); 122 (100); 108 (40); 95 (42); 94 (21); 82 (26); 80 (25); 67 (13); 55 (20); 54 (29); and 41 (13). Anal. calcd for $C_9H_{13}NO_2$ (167.21): C, 64.65; H, 7.84; N, 8.38; found C, 64.76; H, 7.95; N, 8.31.

4.2.2. 3-Ethyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3] oxazin-1-one 11b. Flash chromatography (petrol ether/EtOAc 3/2, R_f=0.44). Yield: 52%, yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1674. ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (3H, t, J=7.4 Hz, CH_3); 1.70–1.80 (2H, m, CH_3CH_2); 1.80–1.97 (2H, m, NCH_2CH_2); 2.04–2.14 (2H, m, $N(CH_2)_2CH_2$); 2.22–2.51 (2H, m, $NCCH_2$); 3.50 (1H, ddd, J=4.4, 8.5, 12.9 Hz, (*H*CH)N); 3.89 (1H, ddd, J=4.4, 5.4, 12.9 Hz, (HC*H*)N); 4.09–4.21 (1H, m, CHO); and 4.69 (1H, br s, NC=CH). ^{13}C NMR (75 MHz, $CDCl_3$): 9.3 (CH_3); 21.8 and 21.9 ($NCH_2(CH_2)_2$); 27.5 (CH_2CH_3); 32.7 ($NCCH_2$); 42.9 (CH_2N); 77.3 (OCH); 103.6 (NC=*C*H); 131.4 (N*C*=CH); and 151.7 (C=O). MS (70 eV) *m*/*z* (%): 181 (M^+, 88); 152 (8); 136 (87); 122 (100); 108 (49); 96 (17); 95 (20); 94 (32); 82 (22); 81 (16); 80 (24); 67 (13); 55 (23); 54 (22); and 41 (14). Anal. calcd for $C_{10}H_{15}NO_2$ (181.23): C, 66.27; H, 8.34; N, 7.73; found C, 66.41; H, 8.24; N, 7.61.

4.2.3. 3-Benzyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3] oxazin-1-one 11c. Flash chromatography (petrol ether/EtOAc 3/2, R_f=0.58). Yield: 60%, white crystals, mp 186–188 °C. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1673. ^1H NMR (300 MHz, $CDCl_3$): δ 1.79–1.89 (2H, m, NCH_2CH_2); 2.05–2.17 (2H, m, $N(CH_2)_2CH_2$); 2.30–2.44 (2H, m, $NCCH_2$); 2.85 and 3.11 (2H, 2×dd, J=5.4, 7.7, 13.7 Hz, (HCH)C_6H_5); 3.52 (1H, ddd, J=4.3, 8.5, 12.9 Hz, (*H*CH)N); 3.87 (1H, ddd, J=4.3, 5.9, 12.9 Hz, (HC*H*)N); 4.40–4.49 (1H, m, OCH); 4.65–4.66 (1H, m, NC=CH); and 7.20–7.39 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): 21.8 ($NCH_2(CH_2)_2$); 32.2 ($NCCH_2$); 40.8 ($CH_2C_6H_5$); 42.9 (CH_2N); 76.5 (OCH); 104.1 (NC=*C*H); 127.0 (HC_{para}); 128.7 and 129.6 (2×HC_{ortho} and 2×HC_{meta}); 131.0 (N*C*=CH); 136.0 ($C_{arom,quat}$); and 151.3 (C=O). MS (70 eV) *m*/*z* (%): 243 (M^+, 85); 199 (12); 198 (57); 184 (5); 170 (5); 122 (18); 108 (100); 97 (14); and 91 (33). Anal. calcd for $C_{15}H_{17}NO_2$ (243.30): C, 74.05; H, 7.04; N, 5.76; found C, 73.95; H, 7.14; N, 5.85.

4.2.4. 3-Isopropyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one 11d. Flash chromatography (petrol ether/EtOAc 3/2, R_f=0.60). Yield: 48%, yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1677. ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 and 1.02 (6H, 2×d, J=6.9 Hz, $(CH_3)_2$); 1.75–1.94 (3H, m, NCH_2CH_2 and $CHMe_2$); 2.05–2.12 (2H, m, $N(CH_2)_2CH_2$); 2.33–2.53 (2H, m, $NCCH_2$); 3.46 (1H, ddd, J=4.1, 8.8, 12.9 Hz, (*H*CH)N); 3.89–3.97 (2H, m, (HC*H*)N and OCH); and 4.68–4.71 (1H, m, NC=CH). ^{13}C NMR (75 MHz, $CDCl_3$): 17.7 and 17.8 ($(CH_3)_2$); 21.8 ($NCH_2(CH_2)_2$); 30.3 ($NCCH_2$); 32.8 ($CHMe_2$); 42.8 (CH_2N); 80.7 (OCH); 103.5 (NC=*C*H); 131.5 (N*C*=CH); and 151.9 (C=O). MS (70 eV) *m*/*z* (%): 195 (M^+, 42); 150 (26); 136 (100); 122 (10); 110 (12); 108 (32); 94 (10); 80 (6); 55 (10); and 54 (8). Anal. calcd for $C_{11}H_{17}NO_2$ (195.26): C, 67.66; H, 8.78; N, 7.17; found C, 67.51; H, 8.85; N, 7.28.

4.2.5. 3-Isobutyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one 11e. Flash chromatography (petrol ether/EtOAc 3/2, R_f=0.62). Yield: 70%, yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1673. ^1H NMR (300 MHz, $CDCl_3$): δ 2×0.93 (6H, 2×d, J=6.6 Hz, $(CH_3)_2$); 1.62–1.71 (2H, m, CH_2CHMe_2); 1.79–1.92 (3H, m, NCH_2CH_2 and $CHMe_2$); 2.05–2.07 (2H, m, $N(CH_2)_2CH_2$); 2.27–2.50 (2H, m, $NCCH_2$); 3.51 (1H, ddd, J=4.8, 8.1, 12.9 Hz, (*H*CH)N); 3.88 (1H, ddd, J=4.8, 5.3, 12.9 Hz, (HC*H*)N); 4.26–4.35 (1H, m, OCH); and 4.69 (1H, br s, NC=CH). ^{13}C NMR (75 MHz, $CDCl_3$): 21.7 and 21.8 ($NCH_2(CH_2)_2$); 22.1 and 22.9 ($(CH_3)_2$); 23.9 ($CHMe_2$); 33.6 ($NCCH_2$); 42.9 and 43.5 (CH_2CHMe_2 and CH_2N); 74.4 (OCH); 103.6 (NC=*C*H); 131.3 (N*C*=CH); and 151.7 (C=O). MS (70 eV) *m*/*z* (%): 209 (M^+, 58); 164 (15); 152 (23); 150 (55); 122 (100); 108 (19); and 97 (47). Anal. calcd for $C_{12}H_{19}NO_2$ (209.14): C, 68.87; H, 9.15; N, 6.69; found C, 68.76; H, 9.27; N, 6.80.

4.2.6. 3-(4-Methoxybenzyl)-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one 11f. Flash chromatography (petrol ether/EtOAc 3/2, R_f=0.42). Yield: 46%, oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1684. ^1H NMR (300 MHz, $CDCl_3$): δ 1.77–1.91 (2H, m, NCH_2CH_2); 1.99–2.12 (2H, m, $N(CH_2)_2CH_2$); 2.26–2.43 (2H, m, $NCCH_2$); 2.79 and 3.04 (2H, 2×dd, J=5.2, 7.7, 13.8 Hz, (HCH)C_6H_5); 3.51 (1H, ddd, J=4.3, 8.5, 12.8 Hz, (*H*CH)N); 3.80 (3H, s, OCH_3); 3.87 (1H, ddd, J=4.3, 5.2, 12.9 Hz, (HC*H*)N); 4.35–4.44 (1H, m, OCH); 4.64 (1H, br s, NC=CH); 6.83–6.86 (2H, m, 2×HC_{ortho}); and 7.11–7.15 (2H, m, 2×HC_{meta}). ^{13}C NMR (75 MHz, $CDCl_3$): 21.8 ($NCH_2(CH_2)_2$); 32.1 ($NCCH_2$); 39.8 ($CH_2C_6H_5$); 42.9 (CH_2N); 55.4 (OCH_3); 76.7 (OCH); 103.9 (NC=*C*H); 114.1 (2×HC_{ortho}); 130.6 (2×HC_{meta}); 127.9 and 131.1 (N*C*=CH and $C_{arom,quat}$); and 158.7

(C=O). MS (70 eV) *m/z* (%): 273 (M^+, 83); 229 (25); 228 (65); 152 (22); 134 (21); 124 (21); 122 (19); 121 (86); 108 (100); 97 (19); and 77 (12). Anal. calcd for $C_{16}H_{19}NO_2$ (273.33): C, 70.31; H, 7.01; N, 5.12; found C, 70.20; H, 7.16; N, 5.23.

4.2.7. (3*R,5*S**)- and (3*R**,5*R**)-3-Methylhexahydropyrido[1,2-*c*][1,3]oxazin-1-one 2a.** *Method A*: To an ice-cooled solution of 3-methyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one **11a** (170 mg, 1.0 mmol) in 20 mL of dry MeOH, $NaCNBH_3$ (188 mg, 3.0 mmol) and glacial AcOH (90 mg, 1.5 mmol) were added. The reaction mixture was stirred for 72 h under reflux, then poured into water (30 mL) and extracted with CH_2Cl_2 (3×40 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel with hexane/EtOAc (3/2, R_f=0.55), resulting in an inseparable mixture of *cis* and *trans* **2a** (*cis*/*trans*=86/14). The ^{1}H NMR peaks of the two isomers overlapped for all protons except H-8. The minor component could only be detected by GC, ^{1}H NMR and ^{13}C NMR. *Method B*: To an ice-cooled solution of **11a** (36 mg, 0.21 mmol) in 5 mL of glacial AcOH, $NaBH_4$ (30 mg, 0.84 mmol) was added. The reaction mixture was next allowed to warm up to room temperature, stirred for 5 h at this temperature, poured into water (10 mL) and extracted with $CHCl_3$ (3×25 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was analysed by ^{1}H NMR; and the *cis*/*trans* ratio was found to be the same as in *Method A*.

Yield (*cis*/*trans*=86/14): 136 mg (80%), semisolid. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1691. *Major isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16–2.00 (7H, m); 1.33 (3H, d, J=6.2 Hz, CH_3); 2.06 (1H, ddd, J=2.0, 5.5, 14.1 Hz, C*H*$_2$CHO); 2.66 (1H, dt, J=2.5, 12.6 Hz, N(HC*H*)(CH$_2$)$_3$); 3.24–3.33 (1H, m, N(CH$_2$)$_4$C*H*); 4.24–4.43 (1H, m, CHO); and 4.44–4.50 (1H, m, N*H*CH(CH$_2$)$_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$): 21.5 (CH_3); 24.3 and 25.6 (NCH$_2$(*C*H$_2$)$_2$); 34.2 (NCH*C*H$_2$); 38.2 (N(CH$_2$)$_3$*C*H$_2$); 45.3 (N*C*H$_2$(CH$_2$)$_3$); 54.6 (NCH); 72.0 (CHO); and 154.3 (C=O). MS (70 eV) *m/z* (%): 170 (M^++1, 14); 169 (M^+, 76); 127 (100); 126 (85); 83 (64); and 68 (18). *Minor isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.24–4.41 (1H, m, N*H*CH(CH$_2$)$_3$), all the other peaks overlapped with the peaks of the major compound. ^{13}C NMR (100.6 MHz, $CDCl_3$): 21.2 (CH_3); 25.2 and 26.1 (NCH$_2$(*C*H$_2$)$_2$); 33.8 (NCH*C*H$_2$); 35.5 (N(CH$_2$)$_3$*C*H$_2$); 46.4 (N*C*H$_2$(CH$_2$)$_3$); 53.8 (N*C*H); 70.5 (*C*HO); and 154.1 (*C*=O). Anal. calcd for $C_9H_{15}NO_2$ (169.22): C, 63.88; H, 8.93; N, 8.28; found C, 63.72; H, 8.83; N, 8.41.

4.2.8. (3*R,5*S**)- and (3*R**,5*R**)-3-Ethylhexahydropyrido[1,2-*c*][1,3]oxazin-1-one 2b.** *Method A*: To an ice-cooled solution of 3-ethyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one **11b** (80 mg, 0.44 mmol) in 10 mL of dry MeOH, $NaCNBH_3$ (90 mg, 0.13 mmol) and glacial AcOH (42 mg, 0.66 mmol) were added. The reaction mixture was stirred for 20 h under reflux, then poured into water (10 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel with *n*-hexane/EtOAc 3/2, (R_f=0.58), resulting in an inseparable mixture of *cis* and *trans* **2b** (*cis*/*trans*=88/12). Yield: 80 mg (95%), semisolid. *Method B*: To the ice-cooled solution of **11a** (55 mg, 0.3 mmol) in 8 mL of glacial AcOH, $NaBH_4$ (43 mg, 1.2 mmol) was added. The reaction mixture was allowed to warm up to room temperature, stirred for 5 h at this temperature, poured into water (15 mL) and extracted with $CHCl_3$ (3×30 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was analysed by ^{1}H NMR; the *cis*/*trans* ratio and yield were found to be the same as in *Method A*.

Yield (*cis*/*trans*=88/12): 80%, semisolid. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1688. *Major isomer*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (3H, t, J=7.6 Hz, C*H*$_3$); 1.25–1.56 (2H, m, NCH$_2$C*H*$_2$); 1.69–1.73 (2H, m, C*H*$_2$CH$_3$); 1.77–1.90 (2H, m, N(CH$_2$)$_2$C*H*$_2$); 1.98 (2H, dd, J=4.5, 13.6 Hz, NCHC*H*$_2$); 2.18–2.23 (2H, m, N(CH$_2$)$_3$C*H*$_2$); 2.58 (1H, dt, J=2.5, 12.8 Hz, N(HC*H*)(CH$_2$)$_3$); 3.13–3.26 (1H, m, CHO); 3.94–4.03 (1H, m, N(CH$_2$)$_4$C*H*); and 4.40 (1H, m, N*H*CH(CH$_2$)$_3$). ^{13}C NMR (68 MHz, $CDCl_3$): 9.1 (CH_3); 23.7 and 25.1 (NCH$_2$(*C*H$_2$)$_2$); 27.9 (*C*H$_2$CH$_3$); 33.6 (NCH*C*H$_2$); 35.3 (N(CH$_2$)$_3$*C*H$_2$); 44.7 (N*C*H$_2$(CH$_2$)$_3$); 54.0 (NCH); 76.3 (CHO); and 154.1 (C=O). MS (70 eV) *m/z* (%): 184 (M^++1, 18); 183 (M^+, 95); 168 (9); 154 (65); 140 (85); 138 (36); and 127 (100). *Minor isomer*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (3H, t, J=7.4 Hz, C*H*$_3$); 1.25–1.56 (2H, m, NCH$_2$C*H*$_2$); 1.74–1.76 (2H, m, C*H*$_2$CH$_3$); 1.77–1.90 (2H, m, N(CH$_2$)$_2$C*H*$_2$); 2.02–2.07 (2H, m, NCHC*H*$_2$); 2.28–2.31 (2H, m, N(CH$_2$)$_3$C*H*$_2$); 2.51–2.65 (1H, m, overlapped, N(HC*H*)(CH$_2$)$_3$); 3.13–3.26 (1H, m, N(CH$_2$)$_4$C*H*); 4.04–4.13 (1H, m, CHO); and 4.33 (1H, d, J=13.6 Hz, N*H*CH(CH$_2$)$_3$). ^{13}C NMR (68 MHz, $CDCl_3$): 9.4 (CH_3); 24.6 and 25.5 (NCH$_2$(*C*H$_2$)$_2$); 27.6 (*C*H$_2$CH$_3$); 32.7 (NCH*C*H$_2$); 33.2 (N(CH$_2$)$_3$*C*H$_2$); 45.8 (N*C*H$_2$(CH$_2$)$_3$); 53.2 (N*C*H); 75.0 (CHO); and 154.1 (C=O). Anal. calcd for $C_{10}H_{17}NO_2$ (183.25): C, 65.54; H, 9.35; N, 7.64; found C, 65.45; H, 9.42; N, 7.56.

4.2.9. (3*R,5*S**)-3-Benzylhexahydropyrido[1,2-*c*][1,3]oxazin-1-one 2c.** To an ice-cooled solution of 3-benzyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one **11c** (50 mg, 0.21 mmol) in 5 mL of glacial AcOH, $NaBH_4$ (30 mg, 0.84 mmol) was added. The reaction mixture was then allowed to warm up to room temperature and stirred for 3 h at this temperature, poured into water (10 mL) and extracted with $CHCl_3$ (3×25 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel with *n*-hexane/EtOAc (3/2, R_f=0.70) resulting in **2c**, as the *cis* isomer only. Yield: 40 mg (80%), mp 88–89 °C.

IR (NaCl, cm^{-1}): ν_{max}=3324, 1673, 1436, 1154, and 796. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15–1.52 (4H, m, N(CH$_2$)(*H*CH)$_3$HC(*H*CH)); 1.66–1.99 (4H, m, N(CH$_2$)(HC*H*)$_3$HC(HC*H*)); 2.62 (1H, dt, J=2.7, 13.4 Hz, N(HC*H*)(CH$_2$)$_3$); 2.86 and 3.07 (2H, 2×dd, J=5.0, 8.1, 13.6 Hz, C*H*$_2$C$_6$H$_5$); 3.15–3.24 (1H, m, N(CH$_2$)$_4$C*H*); 4.27–4.38 (1H, m, CHO); 4.46 (1H, dt, J=13.1 Hz, overlapped peaks, N*H*CH(CH$_2$)$_3$); and 7.21–7.32 (5H, m, C$_6$H$_5$). ^{13}C NMR (68 MHz, $CDCl_3$): 24.3 and 25.6 (NCH$_2$(*C*H$_2$)$_2$); 34.2 (N(CH$_2$)$_3$*C*H$_2$); 35.6 (*C*H$_2$CH(O)); 42.0 (*C*H$_2$C$_6$H$_5$); 45.4 (N*C*H$_2$(CH$_2$)$_3$); 76.3 (CHO); 127.5 (HC$_{para}$); 129.2, 130.2 (2×HC$_{ortho+meta}$);

136.9 (Cq_{arom}); and 151.3 (C=O). MS (70 eV) *m/z* (%): 246 ($M^+ + 1$, 3); 245 (M^+, 11); 201 (65); 110 (54); and 83 (100). Anal. calcd for $C_{15}H_{19}NO_2$ (245.32): C, 73.44; H, 7.81; N, 5.71; found C, 73.60; H, 7.76; N, 5.80

4.2.10. (2*R,2′*S**)-1-(*N*-Methylpiperidin-2-yl)propan-2-ol 1a.** To a slurry of $LiAlH_4$ (100 mg, 2.6 mmol) in 10 mL of dry THF, a diastereomeric mixture of *cis*- and *trans*-3-methylhexahydropyrido[1,2-*c*][1,3]oxazin-1-one **2a** (220 mg, 1.3 mmol) dissolved in 4 mL of dry THF was added dropwise at room temperature. The reaction mixture was stirred for 1 h under reflux, and the excess of $LiAlH_4$ was then decomposed by addition of 0.20 g of water in 2 mL of THF. The inorganic part was filtered off and washed with THF and the organic phase was dried ($MgSO_4$), filtered and evaporated in vacuo to yield the crude product, as 190 mg of a pale-yellow oil. NMR study of the crude product revealed the presence of two isomers in a ratio of 86:14. After purification by flash chromatography with CH_2Cl_2/triethylamine (9/1, R_f=0.25) on silica gel, only the major isomer was isolated in diastereomeric pure form, and identified as *N*-methylallosedridine. Yield: 135 mg, 66%. The ^1H and ^{13}C NMR data corresponded to those of *N*-methylallosedridine in the literature.[19]

NMR (400 MHz, $CDCl_3$): δ 1.16 (3H, d, J=6.3 Hz); 1.19–1.61 (5H, m); 1.65–1.73 (2H, m); 2.42 (3H, s); 2.44–2.51 (1H, m); 2.59–2.65 (1H, m); 2.98 (1H, ddd, J=3.0, 7.0, 9.6 Hz); and 3.97 (1H, dqd, J=2.5, 6.1, 10.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): 21.3; 22.7; 24.5; 26.5; 39.4; 40.2; 52.4; 60.8; and 67.9.

4.2.11. (2*R,2′*S**)-(1-(*N*-Methylpiperidin-2-yl)butan-2-ol 1b.** To an ice-cooled solution of a diastereomeric mixture of *cis*- and *trans*-3-ethylhexahydropyrido[1,2-*c*][1,3]oxazin-1-one **2b** (50 mg, 0.28 mmol) in 10 mL of dry Et_2O, $LiAlH_4$ (26 mg, 0.7 mmol) was added. The reaction mixture was stirred for 4 h under reflux and then poured into ice cold water. The organic phase was separated, dried ($MgSO_4$), filtered and evaporated in vacuo to yield the crude product. This product was purified by flash chromatography with CH_2Cl_2/triethylamine 9/1 (R_f=0.18), resulting in 1-(*N*-methylpiperidin-2-yl)butan-2-ol **1b**. Only the major isomer was identified after the purification process.[19]

Yield: 30 mg (65%). IR (NaCl, cm^{-1}): ν_{C-OH}=3419 cm^{-1}; ν_{max}=2935; 2856; 2795; 2087; 1645; 1458; 1376; 1268; 1121; 1022; and 983. ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (3H, t, J=7.3 Hz CH_2CH_3); 1.16–1.45 (5H, m, $N(CH_2)(HCH)_3HC(CH_2)$); 1.47 (2H, q, J=7.1 Hz, CH_2CH_3); 1.52–1.87 (3H, m, $N(CH_2)(HCH)_3$); 2.42 (3H, s, N–CH_3); 2.45–2.55 (1H, m, $N(HCH)(CH_2)_3$); 2.56–2.75 (1H, m, $N(CH_2)_4CH$); 2.97–3.04 (1H, m, $N(HCH)(CH_2)_3$); 3.66–3.74 (1H, m, CH(OH)); and 4.36–4.38 (1H, d, J=7.98 Hz, CH(O*H*)). ^{13}C NMR (68 MHz, $CDCl_3$): 9.9 (CH_3); 20.9 and 22.7 ($NCH_2(CH_2)_2$); 26.3 CH_2CH_3); 31.2 ($NCHCH_2CH$(OH)); 37.1 ($N(CH_2)_3CH_2$); 40.1 (N–CH_3); 51.9 ($NCH_2(CH_2)_3$); 60.9 ($N(CH_2)_4CH$); and 73.5 (CH(OH)). MS (70 eV) *m/z* (%): 171 (M^+,1); 142 (5); 112 (2); 98 (100); 84 (2); 70 (9); 57 (3); and 42 (5).

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