Alkylation of N,N-Dibenzylaminoacetonitrile: From Five- to Seven-Membered Nitrogen-Containing Heterocyclic Systems

Jacques Renault, Christelle Bouvry, Jean-François Cupif, Jean-Pierre Hurvois

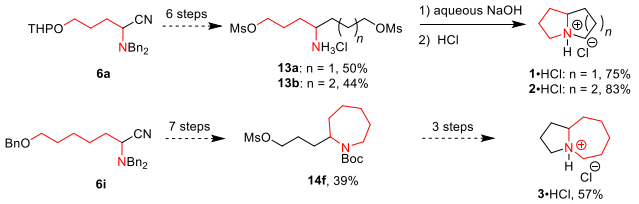
Alkylation of *N*,*N*-dibenzylaminoacetonitrile: From five to seven membered nitrogen containing heterocyclic systems.

Jacques Renault,[a] Christelle Bouvry,[b] Jean-François Cupif,[a] Jean-Pierre Hurvois*[a]

[a] Univ Rennes, CNRS, ISCR (Institut des Sciences Chimiques Rennes), UMR 6226, F-35000 Rennes, France.

[b] Comprehensive Cancer Center Eugène Marquis, Avenue de la Bataille Flandre-Dunkerque, 35000, Rennes, France.

Abstract.



The syntheses of several alkaloids and nitrogen containing compounds including *N*-Boc-coniine (**14b**), pyrrolizidine (**1**), δ-coniceine (**2**) and pyrrolo[1,2a]azepine (**3**) are described. New C-C bonds in the α position relative to the nitrogen atom were formed by the alkylation of metalated α-aminonitriles **4** and **6a-c** with alkyl iodides possessing the requisite size and functionality. In all the reported cases, the pyrrolidine ring was formed in the aqueous medium through a favorable 5-exo-tet process involving a primary or a secondary amino group and a terminal δ-leaving group. Conversely, the azepane ring was efficiently formed in DMF, as the preferred aprotic solvent, through an unreported 7-exo-tet cyclization process involving a more nucleophilic sodium amide and a terminal mesylate borne by a saturated 6 carbon chain unit. In this way, we successfully synthesized pyrrolo[1,2a]azepane **3** and 2-propyl-azepane **14c** in good yields from inexpensive and readily available materials without tedious separation methods.

Introduction

Alkaloids form a large group of molecules that are found in both the animal and vegetal kingdoms.[1] Among them, the izidine alkaloids constitute a group of nearly 800 compounds that display fused bicyclic nitrogen-containing systems, such as pyrrolizidine, indolizidine, or quinolizidine.[2] Pyrrolizidine alkaloids have been mainly isolated from plants of the Astereaceae, Boraginaceae, or Fabaceae family.[3] In contrast, indolizidine alkaloids have not only been isolated from plants, but also from the skin of amphibians belonging to the Dendrobatidae or Bufonidae family.[4] In addition to their natural occurrence, pyrrolizidine alkaloids display a wide range of biological activities. For example, polyhydroxylated pyrrolizidines such as (–)-alexine or (+)-hyacinthacine B1 (Figure 1) proved to be potent inhibitors of glycosidase, resulting in cytotoxic, fungicidal, and antiviral effects.[5] Indolizidine alkaloids also display a myriad of biological properties. For example, tylophorine and related phenanthrene-based analogs, present antiproliferative effects against various cell lines,[6] whereas the lipophilic alkaloid gephyrotoxine presents antimuscarinic effects and selectively inhibits the postsynaptic nicotinic Ach receptor channels.[7] Conversely, the pyrrolo[1,2*a*]azepine ring system has been found in a restricted number of natural products, such as alkaloid 275A,[8] or (–)-cephalotaxine which proved to be efficient in the treatment of chronic myeloid leukemia.[9]

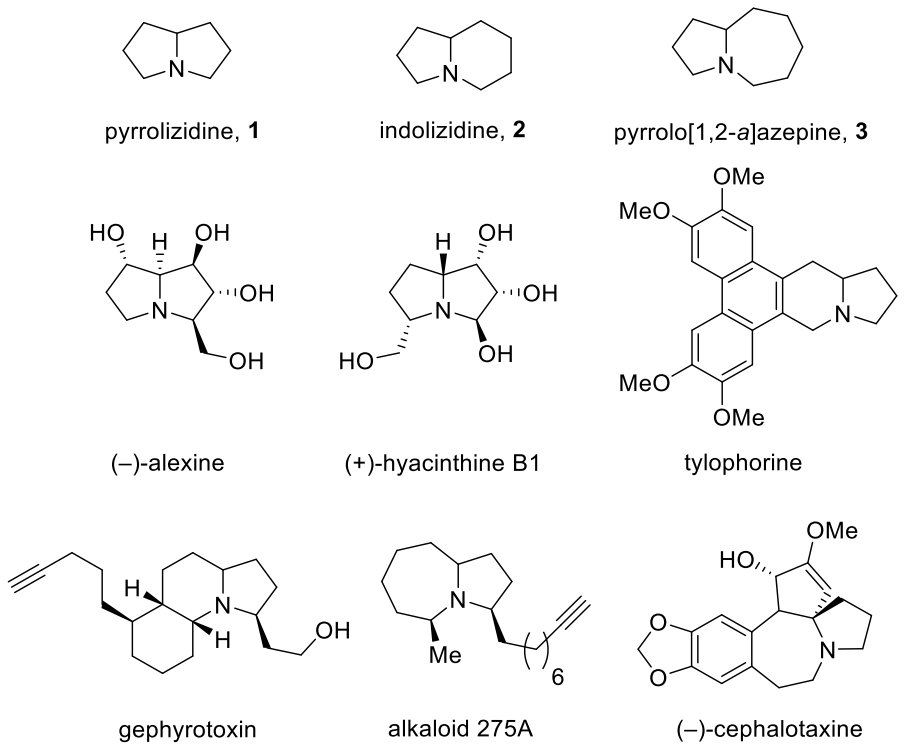
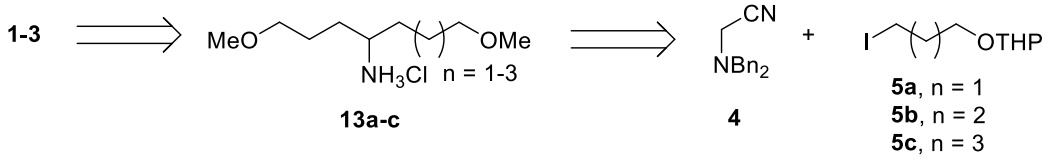


Figure 1. Structures of pyrrolizidine (**1**), indolizidine (**2**), pyrrolo1,2*a*]azepine (**3**), and natural products that contain these structural systems.

The aforementioned biological activities have attracted the attention of chemists to propose synthetic routes to azabicyclic systems **1–3**. In the last two decades, strategies for the construction of pyrrolizidine **1** or racemic δ-coniceine **2** have included the alkylation of 2-methyl-1-pyrrolines,[10] organocatalytic α-amination of aldehydes,[11] hydrogenation of pyrrolizin-3-ones,[12] ring contraction of methyl-(*E*)-[1,2-oxazin-3-yl]propenoates,[13] Pummerer cyclization,[14] Aza-Prins cyclization,[15] decarboxylation of α-tertiary amino acids,[16] photooxygenation of furylalkylamines,[17] Heck cyclization of enamides,[18] and intramolecular aldol condensation of activated imides.[19]

In contrast, approaches devoted to the synthesis of pyrrolo[1,2a]azepines have been reported on scarce occasions mainly because of the difficulty in synthesizing the azepane ring due to the loss of entropy upon cyclization, which is not counterbalanced by ring stability.[20] Nevertheless, recent and former approaches to molecule **3** were based on the cyclization of acyclic precursors through reductive amination, ring closing metathesis reaction,[21] silver induced bicyclizations, rearrangement of *N*-chloramines,[22] cyclization of primary amines,[23] and pyrolysis of cycloalkano[*a*]pyrroles.[24] Although successful, the syntheses of derivatives **1–3** may require many steps and reagents, the handling of toxic molecules (*e.g*. *N*-chloramines), or the preparation of complex precursors and sometimes harsh reaction conditions. Consequently, the elaboration of a general synthetic approach to these pivotal heterocyclic systems is a challenging task. For the present work, it was necessary to design linear precursors allowing a bicyclization process between a primary amine (or its synthetic equivalent) and two leaving groups borne by saturated carbon chains. The retrosynthetic analysis is delineated in Scheme 1 and is based on the iterative alkylation of dibenzylaminonitrile **4** with bifunctional alkyl iodides **5a-c** to form mesylates **13** and their use as efficient building blocks for the synthesis of bicyclic systems **1-3**.



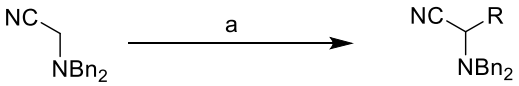
Scheme 1. Retrosynthesis of bicyclic derivatives **1-3** from mesylates **13a-c**.

Results and discussion

Synthesis of α-aminonitriles 6c-h.

This work began with the synthesis of α-aminonitriles **6c-h** (Table 1) according to a reaction sequence that has been reported previously for the preparation of α-aminonitriles **6a,b**.[25] To gain

further insight into the reactivity of lithiated α-aminonitrile **4**, several condensation experiments were carried out in the presence of iodides with increasing length (**5d-h**). There are two distinct steps for this process: the initial deprotonation of α-aminonitrile **4** and the alkylation of the resulting carbanion.[26] For comparison, all the experiments were performed in the presence of 1.25 equivalents of LDA as the base and THF as the solvent.



4 **6**

Entry	Alkylating Agent (RI)	Product, n°	Yield (%)[a]
1	I-$(CH_2)_3$-OTHP (**5a**)	**6a**	78
2	I-$(CH_2)_4$-OTHP (**5b**)	**6b**	83
3	I-$(CH_2)_5$-OTHP (**5c**)	**6c**	85
4	I-C_3H_7 (**5d**)	**6d**	76
5	I-C_5H_{11} (**5e**)	**6e**	81
6	I-C_7H_{15} (**5f**)	**6f**	80
7	I-$C_{11}H_{23}$ (**5g**)	**6g**	78
8	I-$C_{14}H_{29}$ (**5h**)	**6h**	72

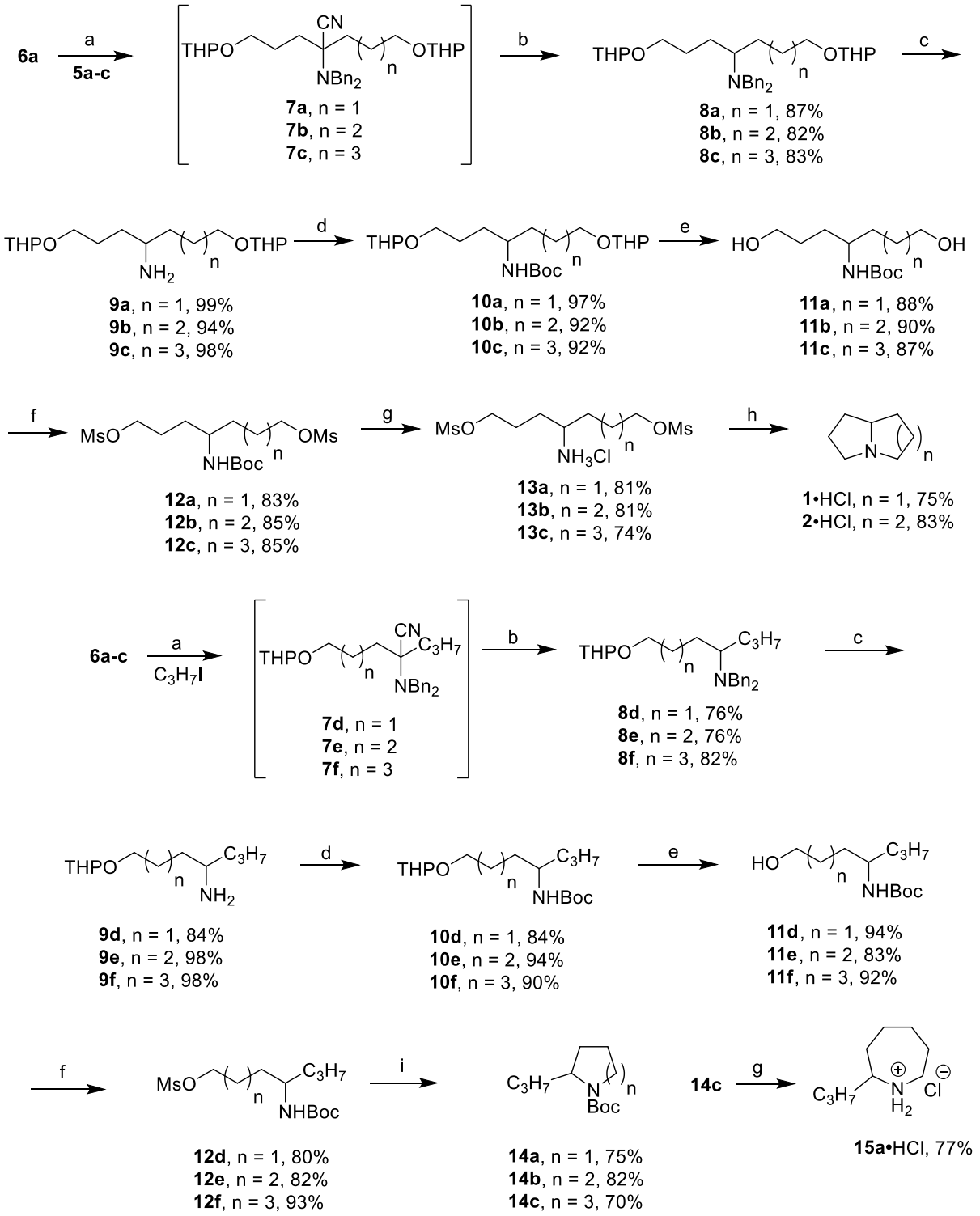
Table 1. Synthesis of α-aminonitriles **6a-h**. Reagents and conditions: a: LDA (1.25 equiv.), THF, –80 °C to –30 °C, 1.5 h, then RI, –80 °C to 30 °C, 1.5 h. [a]Yields are given for the isolated products.

The deprotonation step was carried out upon the rapid addition of LDA at –80 °C to instantaneously produce a deep-red solution that was warmed to –30 °C over a 1.5 h period. The resulting anion solution was cooled to –80 °C before the addition of 1.1 equivalents of iodides **5a-h**, causing the discoloration of the medium and the transient precipitation of lithium iodide. After aqueous work-up, and chromatographic purification, α-aminonitriles **6a-h** were obtained in yields ranging from 72% to 85%. Upon comparing entries 3 and 5, one sees that the presence of an oxygenated moiety on the electrophile **5c** has little effect, while the condensation seems to be quite insensitive to the length of the electrophiles (entries 4-8) which clearly indicates that lithiated α-aminonitrile **4** is highly nucleophilic.[27] Having installed the requisite chains in **4**, we next turned to the synthesis of bicyclic derivatives **1-3**.

Synthesis of bicyclic derivatives 1,2 and 2-propyl derivatives 14a-c.

For the synthesis of amines **8a-c** (Scheme 2, top), we believe the best approach is the alkylation of α-aminonitrile **6a** in the presence of iodides **5a-c**. The conversion was accomplished according to the same stoichiometric parameters of the previous alkylation protocol. After work-up, we isolated the expected fully substituted α-aminonitriles **7a-c** together with unreacted material (up to 5-10%), which could be differentiated in ^{1}H NMR spectroscopy by the distinct resonance signals of the CH protons of the *O*,*O*-acetal groups, which resonated as a triplet (*J* = 4.60 Hz) at δ = 4.42 ppm in α-aminonitrile **6a**. In addition, close examination of the ^{1}H NMR spectrum of the **6a** to **7a** transformation, revealed the presence of ethylenic resonance signals which were attributed to the presence (up to 10%) of 2-(allyloxy)tetrahydro-2*H*-pyran, indicating that an elimination process (*E*2) occurred between lithiated α-aminonitrile **6a** and iodide **5a**. Note that similar observations were made during the **6a** to **7b,c** condensations. We also reasoned that the utilization of an excess of base and electrophile, together with prolonged stirring at a lower temperature would improve the conversion yield and S_N/*E*2 ratio, respectively. Following these data, the deprotonation of **6a** was carried out in the presence of 1.60 equivalents of LDA for a 2 h period upon which 1.30 equivalents of iodides **5a-c** were added at –80 °C. The resulting mixture was slowly warmed to –20 °C for 3 h to produce α-aminonitriles **7a-c** as the sole products, which could not be purified by column chromatography due to their instability on silica. These encouraging results prompted us to evaluate the reactivity of metalated α-aminonitriles **6a-c** involving 1-iodopropane as the electrophile (Scheme 2, middle). The reaction sequence was carried out as depicted above to cleanly produce quaternary α-aminonitriles **7d-f** in nearly quantitative yields. We next turned to the removal of the nitrile group from α-aminonitriles **7a-f**. The reductive decyanation of quaternary α-aminonitriles consists of the neat replacement of the nitrile group by a hydrogen atom. This process involves a hydride transfer on a transient iminium salt whose formation is best achieved in the presence of borane salts formed in situ.[28] Thus, stirring a mixture of crude α-aminonitriles **7a-f** and 4.0 equivalents of $NaBH_4$ in ethanol for 5 h at rt, followed by a reflux period of 3 h in the presence of an additional 3.0 equivalents of $NaBH_4$, afforded amines **8a-f** in yields ranging from 76% to 86% after chromatographic purification.

With the required amines **8a-f** in hand, we turned to the catalytic hydrogenolysis step which proved to be capricious when the reaction was carried out at rt in methanol under a hydrogen pressure of 5 bars for 72 h in the presence of 20% $Pd/(OH)_2$ (up to 10% in mass) as the catalyst. Under these reaction conditions, the reaction was generally half complete and lacked repeatability. Based on our experience, a second experiment was carried out at 60 °C within the same period and catalyst loading. In this way, primary amines **9** were obtained in nearly quantitative yields and could be used in the next step without further purification.



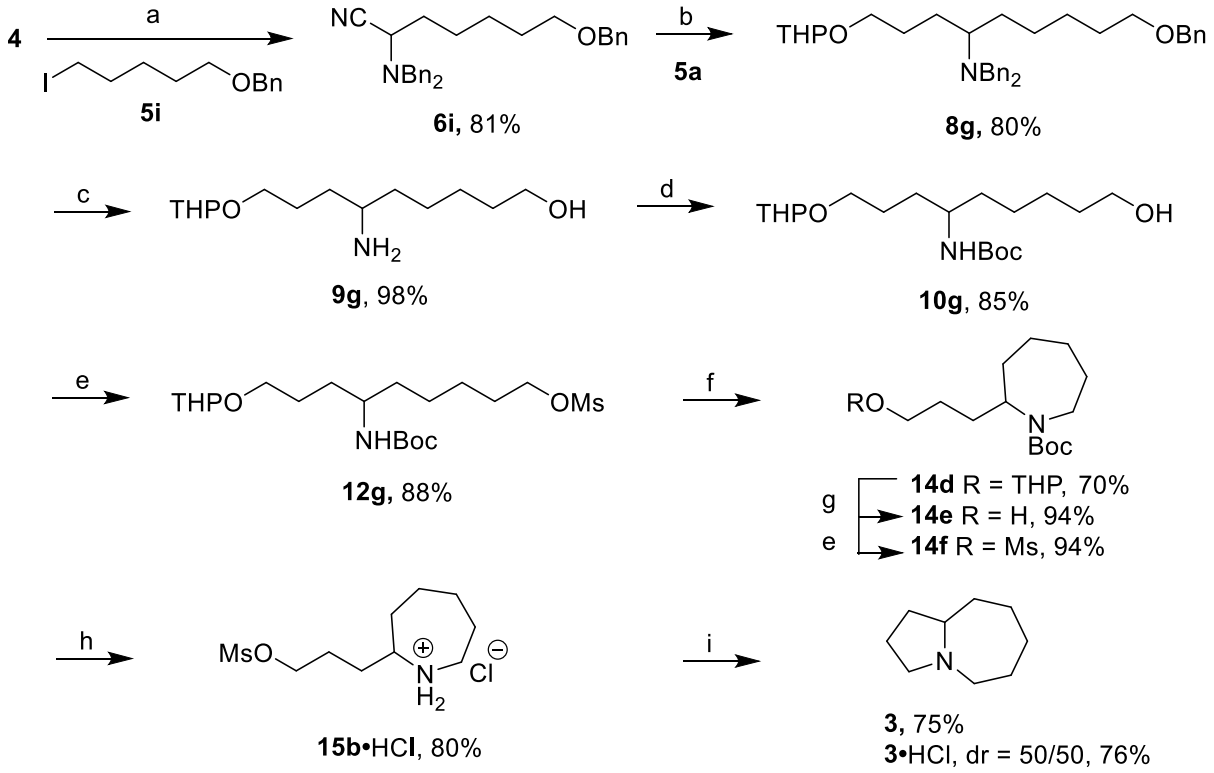
Scheme 2. Synthesis of bicyclic derivatives **1,2** and 2-propyl derivatives **14a-c**. Reagents and conditions: a: 1, LDA (1.60 equiv.), THF, –80 to –20 °C, 2 h, then 2, **5a-c** (1.30 equiv.), –80 °C to –20 °C, 3 h; b: 1, $NaBH_4$ (4 equiv.), EtOH, rt, 12 h, then 2, $NaBH_4$ (1 equiv.), reflux, 3 h; c: 20% $Pd(OH)_2$, EtOH/MeOH (*ca*. 70:30), H_2 (5 bars), 60 °C, 72 h; d: Boc_2O (1.0 equiv.), DCM, rt, 12 h; e: MeOH, PPTS, 20 mol%, 50 °C, 12 h; f: MsCl, Et_3N (3.0 equiv.)/DMAP (0.20 equiv.), CH_2Cl_2, rt, 5 h; g: HCl 2 M, dioxane, rt, 24 h; h: 1, NaOH (3.0 equiv.), water, rt, 12 h, then 2, HCl 2 M, diethyl ether; i*:* 1, NaH (5.8 equiv.) rt, DMF, 2 h, 2, for compound **14c***,* NaH (10.0 equiv.) 75 °C, DMF, 2 h.

Our next efforts were devoted to the installation of the terminal leaving groups and we also believe that the primary amine should be protected as a carbamate.[29] This, was cleanly achieved by stirring primary amines **9** in dichloromethane in the presence of one equivalent of Boc_2O to produce carbamates **10** in 84% to 97% yield after chromatographic purification. Next, the deprotection of the terminal alcohol functions was carried out through a transacetalization process which was cleanly achieved by heating a methanolic solution of carbamates **10** at 50 °C for 12 h in the presence of a catalytic amount (20% in mole) of *p*-toluene sulfonate (PPTS) to produce glycols **12a-c** and alcohols **12d-f** in up to nearly quantitative yields after rapid chromatographic purification. Finally, we selected mesylate esters as the preferred leaving groups, and their synthesis was simply achieved by stirring glycols **12a-c** and alcohols **12d-f** in dichloromethane in the presence of 3 equivalents of mesylchloride and triethylamine and a catalytic amount (0.2 equiv) of dimethylaminopyridine (DMAP) to produce mesylates **12** as the sole products.

For the synthesis of bicyclic derivatives **1-3**, we believe that the best synthetic approach is the one step annulation process between the free amino group and the terminal mesyl esters. We also reasoned that the pyrrolidine nucleus should be formed first through a favorable 5-*exo-tet* process.[30] Thus, prolonged stirring of carbamates **12** in a 2 M HCl solution in dioxane for 24 h afforded hydrochloride salts **13** as solids, which proved to be sensitive to moisture and heating.[31] Nevertheless, the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of these salts were consistent with the proposed structures.[32] For example, characteristic low field signals attributed to the tertiary carbons of hydrochlorides **13a** and **13b**, were recorded at δ = 50.73 and 51.09 ppm, respectively. Then, the treatment of aqueous solutions of mesylates **13a-b** with 3 equivalents of sodium hydroxide caused the progressive appearance oily suspensions which progressively decanted as oils with a characteristic mousy smell. Due to its volatility, pyrrolizidine **1** was isolated as its hydrochloride salt (M.p. = 212 °C) after a rapid treatment by a 2 M HCl diethyl ether solution, and δ-coniceine was collected as an oily residue whose spectral data matched in all aspects with those reported in the literature.[11b] In contrast, this first attempt in synthesizing pyrrolo[1,2a]azepine **3** met with failure probably due to an intractable polymerization process. This result was not predictable from the literature data and was probably due to an unfavorable 7-exo-tet process under these reaction conditions. Inspired by the approach developed by Hammond, who bicyclized the hydrochloride salt of 5-amino-1,10-dibromodecane, a second experiment was carried out under more diluting conditions at a more elevated temperature of 50 °C.[23] Unfortunately, the reaction was again unsuccessful.

For a successful synthesis of **3**, we sought to reverse the reaction sequence by the prior formation of the azepane ring. Scrutinizing the literature, data revealed that cyclization reactions of acyclic precursors have rarely been employed for the synthesis of monocyclic azepine derivatives.[33]

For example, the synthesis of 2-propylazepane **14c** has been carried out through the reductive alkylation of *N*-benzylcaprolactam,[34] or from the addition of Grignard reagents on preformed enamine-zinc complexes.[35] We also reasoned that a nucleophilic displacement of a terminal mesyl group by a more nucleophilic sodium amide would more efficiently form the expected azepane ring. To demonstrate the synthetic value of this method, we set *N*-Boc derivatives **14a-c** as initial targets (Scheme 2 bottom). Thus, when mesylates **12d,e** were treated with an excess of sodium hydride in DMF for two hours at 20 °C, carbamates **14a,b** were obtained in up to 82% yield, while in the case of mesylate **12f**, the reaction was half-complete. However, a rapid procedural optimization provided more consistent yields. Indeed, heating the sample at 70 °C for 2 hours ensured a complete conversion of **12e** and clean formation of azepane **14c** (68%) which upon further treatment with 2 M HCl in dioxane afforded hydrochloride **15a**•HCl, whose melting point (M.p. = 174–175 °C, lit.[33] = 167–168 °C) and spectral data matched the reported literature values.



Scheme 3. Synthesis of pyrrolo[1,2a]azepine **3**. Reagents and conditions. a: 1, LDA, THF, –80 °C to –30 °C, 1.5 h, 2, then **5i**, –80 °C to 30 °C, 1.5 h; b: 1, LDA (1.60 equiv.), THF, –80 to –20 °C, 2 h, 2, then **5a** (1.30 equiv.), –80 °C to –20 °C, 3 h, 3, $NaBH_4$ (4 equiv.), EtOH, rt, 12 h, 4, then $NaBH_4$ (1 equiv.), reflux, 3 h.; c: 20% $Pd(OH)_2$, EtOH/MeOH (*ca*. 70:30), H_2 (5 bars), 60 °C, 72 h; d: Boc_2O (1.0 equiv.), DCM, rt, 12 h; e: MsCl, Et_3N (3.0 equiv.)/DMAP (0.20 equiv.), CH_2Cl_2, rt, 5 h; f: NaH (10 equiv.), DMF, 75 °C, 2 h; g: MeOH, PPTS, 20 mol%, 50 °C, 12 h; h: HCl 2M, dioxane, rt, 24 h; i: 1, NaOH (1.5 equiv.), water, rt, 12 h, 2, then HCl 2 M, diethyl ether.

These encouraging results prompted us to investigate an alternate method for the preparation of pyrrolo-azepine **3** (Scheme 3). The most attractive route to **3** should involve an intermediate displaying a single displaceable ζ-mesyl group for reaction with the nucleophilic amide. It was also desirable to perform the synthesis of this intermediate through a short orthogonal deprotection process. Therefore, benzyl ether **8g** was selected as a suitable precursor with the hope that both benzyl protecting groups will be removed in a single operation.

With these purposes in mind, alkyl iodide **5i** was prepared from a slightly modified procedure from the literature in an overall 70% yield, by monobenzylation of 1,5-pentanediol (NaH/THF) with benzyl bromide to afford the intermediary 5(benzyloxy)-penta-1-ol, which was iodinated by the I_2/PPh_3/imidazole system.[36] Next, the preparation of amine **8g** was straightforward, *i.e.*, the iterative alkylation of dibenzylaminoacetonitrile **4** by iodides **5i** and **5a** to form the corresponding fully substituted α-aminonitrile, whose nitrile group was removed by refluxing it in ethanol in the presence of excess $NaBH_4$ to produce **8g** as highly viscous oil. The removal of the benzyl groups in **8g** proceeded smoothly by the application of the previous protocol used for the synthesis of amines **9a-f**, yielding aminoalcohol **9g** as the sole product, as evidenced from the absence of aromatic signals in the ^{1}H NMR spectrum of the crude reaction material. Then, protection of the primary amine and installation of the terminal leaving group were carried out by the successive treatment of **9g** by one equivalent of Boc_2O and an excess of mesylchloride resulting in the isolation of **12g** in an overall 75% yield from **9g**. The key cyclization event was performed by heating a DMF solution of **12g** for 5 h in the presence of an excess of NaH. The intramolecular displacement of the terminal mesyl group proceeded well, and the expected azepane **14d** was obtained in a satisfactory 70% yield. The ^{1}H NMR spectrum is consistent with the ring formation and included a characteristic 2-H signal that appeared as a triplet (J = 12.5 Hz) at δ = 2.64 ppm (1 H). Additionally, the mass spectra supported the exact formula of $C_{19}H_{35}NO_4Na$ with $[M + Na]^+$ at 364.24583 uma. With the required azepane system in hand, we next address the construction of the pyrrolidine ring system by the established method. Thus, installation of the δ-leaving group was carried out in two steps including the liberation (PPTS (20%)/MeOH) of the alcohol group, which was further mesylated (MsCl/Et_3N/DMAP) to afford compound **14f** in an overall 88% yield from **14d**. In the penultimate step, the removal of the nitrogen protecting group was carried out under acidic conditions (4 M HCl in dioxane), providing hydrochloride salt **15b•**HCl in 80% yield. As expected and observed, the final aqueous treatment of this salt by 1.5 equivalents of powdered NaOH afforded the expected pyrrolo-azepine **3** (75% yield) as a colorless oil whose spectral data (^{1}H and ^{13}C{^{1}H} NMR) matched in all aspects with those reported in the literature.[10] Note that protonation (2 M HCl in diethyl-ether) occurred equally on both faces of pyrrolo-azepine **3** to produce a mixture (*ca*. 50:50) of diastereoisomers, as evidenced

by the examination of the $^{13}C\{^1H\}$ NMR spectrum, which displayed two sets of independent resonance lines. For example, two resonance lines of equal height attributed to the α-CH carbons were recorded at δ = 65.63 and 67.53 ppm.

Conclusion.

In summary, we report the iterative alkylation of dibenzylaminoacetonitrile (**4**) by alkyl iodides displaying the requisite size and functionality. Based on this method, several bicyclic systems, such as pyrrolizidine and δ-coniceine, were synthesized through a bicyclization process involving a primary amine and terminal mesyl groups. Moreover, the method is versatile in terms of the ring size and substitution which allowed the synthesis of pyrrolo[1,2a] azepine **3** in an overall 17% yield from **4**. A part from the generally high yields of the individual steps, this method should be amenable to the synthesis of a set of heterocyclic systems.

Experimental Section

General Techniques: Purification by column chromatography was performed with 70–230 mesh silica gel. TLC analyses were carried out on alumina sheets precoated with silica gel 60 F254; R_f values are given for guidance. The ^1H NMR spectra were recorded with a 500 MHz, a 400 MHz or a 300 MHz spectrometer. The $^{13}C\{^1H\}$ NMR spectra were recorded with a 125 MHz, a 100 MHz or a 75 MHz spectrometer. Structural assignments were made with additional information from gCOSY, gHSQC and gHMBC experiments. High resolution mass spectra were recorded on a Maxis 4G (Bruker Daltonik Gmbh, Bremen, Germany) UHR-TOF mass spectrometer in electrospray positive ionization mode at the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, ScanMAT UAR 2025, Université de Rennes 1). Melting points were measured on a Kofler apparatus, the values reported in °C, and were uncorrected. For air-sensitive reactions, the glassware was oven-dried (90 °C) for 24 h and cooled under a stream of argon before use. All commercially available reagents were used as supplied. Diisopropylamine was distilled from solid potassium hydroxide.

2-(3-Iodopropoxy)tetrahydro-2*H*-pyran, 5a. *Step 1. Synthesis of 3-iodopropan-1-ol.* From an adapted procedure reported in the literature.[37] A 250 mL round-bottom flask, equipped with a reflux condenser and a magnetic bar, was flushed with argon and was successively charged with 100 mL of acetone, 5.30 mL (6.00 g, 63.40 mmol, 1.0 equiv.) of 3-chloropropan-1-ol and 14.25 g (95.07 mmol, 1.5 equiv.) of NaI. The resulting mixture was refluxed under argon for 72 h under a vigorous stirring. The resulting suspension was cooled to room temperature and sodium chloride (*ca*. 3.75 g) was removed by filtration over a fritted glassware. The filtrate was concentrated under reduced pressure, and the resulting paste was taken-up with 150 mL of diethyl ether. The excess of NaI (*ca*. 4.25 g) was

removed by a filtration on a fritted glassware and the ethereal solution was concentrated *in vacuo* to afford an oily brown residue (11.60 g) which was stirred for 30 minutes in a biphasic mixture of dichloromethane (150 mL) and a 0.1 M aqueous solution (100 mL) of sodium sulfite. The organic phase was dried over $MgSO_4$, and concentrated to afford a slightly yellow oily residue which was distilled under reduced pressure (50 °C, 10^{-2} mbar, 75.10^{-4} Torr) to afford 10.95 g (93%) of 3-iodopropan-1-ol as a colorless oil. R_f = 0.50 (petroleum ether/diethyl ether, 50:50). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 3.74 (t, *J* = 6.70 Hz, 2 H), 3.31 (t, *J* = 6.70 Hz, 2 H), 2.04 (quint, *J* = 5.90 Hz, 2 H), 1.71 (s, broad, 1 H). ^{13}C {^{1}H} NMR ($CDCl_3$, 75 MHz) δ = 62.3 (s), 35.5 (s), 3.07 (s). *Step 2. Synthesis of derivative **5a**.* From an adapted procedure reported in the literature.[38] A 200-mL, one necked Schlenk tube, fitted with a magnetic stirring bar, and connected to an argon inlet tube was successively charged with 25 mL of dichloromethane, 14.30 g (76.88 mmol, 1.0 equiv.) of 3-iodopropan-1-ol, 8.40 mL (7.78 g, 92.57 mmol, 1.2 equiv.) of 3,4-dihydro-2*H*-pyran and 1.42 g (5.65 mmol, 10% in mass, 7% in mole) of pyridinium *p*-toluenesulfonate (PPTS) and reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the material was taken-up in 100 mL of diethyl ether and stirred vigorously with 100 mL of an aqueous solution (0.1 M) of sodium sulfite for 30 minutes. The solvent was removed under reduced pressure and the crude reaction mixture was distilled under reduced pressure (65 °C, 10^{-2} mbar, 75.10^{-4} Torr) to afford 18.27 g (88%) of iodide **5a** as a slightly yellow oil. R_f = 0.50 (petroleum ether/diethyl ether, 70:30). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.60 (t, *J* = 2.9 Hz, 1 H), 3.90–3.77 (m, 2 H), 3.53–3.40 (m, 2 H), 3.30 (t, *J* = 6.8 Hz, 2 H), 2.09 (quint, *J* = 6.1 Hz, 2 H), 1.74–1.50 (m, 6 H). ^{13}C {^{1}H} NMR ($CDCl_3$, 75 MHz) δ = 98.8 (t), 66.8 (s), 62.2 (s), 33.6 (s), 30.6 (s), 25.4 (s), 19.4 (s), 3.4 (s). The analytical data agreed with those reported in the literature.[39]

2-(4-Iodobutoxy)tetrahydro-2*H*-pyran, 5b. *Step 1. Synthesis of 2-(4-chlorobutoxy)tetrahydro-2H-pyran.* From an adapted procedure reported in the literature.[40] A 250 mL round-bottom flask, was successively charged with 100 mL of dichloromethane, 2.30 mL (2.50 g, 23.04 mmol, 1.0 equiv.) of 4-chlorobutan-1-ol, 2.51 ml (2.33 g, 27.66 mmol, 1.2 equiv.) of 3,4-dihydro-2*H*-pyran, 0.46 g (1.83 mmol, 8% in mole) of pyridinium *p*-toluenesulfonate (PPTS). The resulting mixture was stirred at ambient temperature for 24 h. The organic phase was stirred with 100 mL of water for 15 minutes and the organic phase was dried over $MgSO_4$, and concentrated to afford 4.22 g (95%) of 2-(4-chlorobutoxy)tetrahydro-2*H*-pyran as a slightly yellow oil which was used in the next step without purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.58 (t, *J* = 3.0 Hz, 1 H), 3.89–3.74 (m, 2 H), 3.58 (t, *J* = 6.50 Hz, 2 H), 3.59–3.54 (m, 2 H), 1.95–1.50 (m, 10 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ = 98.8 (t), 66.6 (s), 62.3 (s), 45.0 (s), 30.7 (s), 29.7 (s), 27.1 (s), 25.5 (s), 19.6 (s). *Step 2. Synthesis of iodide **5b***. A 250 mL round-bottom flask, equipped with a reflux condenser and a magnetic bar, was flushed with argon

and successively charged with 120 mL of acetone, 4.00 g (20.76 mmol) of 2-(4-chlorobutoxy)tetrahydro-2*H*-pyran, 4.65 g (31.05 mmol, 1.5 equiv.) of NaI and 0.21 g (2.02 mmol, 0.10 equiv.) of sodium carbonate. The resulting mixture was refluxed under argon for 72 h under a vigorous stirring. The resulting suspension was cooled to room temperature and sodium chloride (*ca*. 1.70 g) was removed by filtration over a fritted glassware. The filtrate was concentrated under reduced pressure and the resulting paste was taken-up with 150 mL of diethyl ether. The excess of NaI (*ca*. 1.5 g) was removed by a filtration on a fritted glassware and the ethereal solution was stirred with 100 mL of an aqueous solution (0.1 M) of sodium sulfite for 30 minutes. The organic phase was dried over $MgSO_4$, and concentrated to afford a slightly yellow oily residue which was poured into a chromatographic column prepared with 120 g of silica and 90:10 petroleum ether/ethyl acetate. The combined fractions were collected and concentrated to afford 4.77 g (81%) of iodide **5b** as a slightly yellow oil. R_f = 0.75 (petroleum ether/ethyl acetate, 90:10). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.58–4.56 (m, 1 H), 3.87–3.82 (m, 2 H), 3.53–3.48 (m, 1 H), 3.43–3.40 (m, 1 H), 3.23 (t, *J* = 7.0 Hz, 2 H), 2.00–1.90 (m, 2 H), 1.85–1.77 (m, 1 H), 1.75–1.67 (m, 3 H), 1.60–1.50 (m, 4 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ = 99.9 (t), 66.3 (s), 62.4 (s), 30.75 (s), 30.70 (s), 30.6 (s), 25.5 (s), 19.7 (s), 6.8 (s). IR (film, cm^{-1}): 868, 1029, 2938. HRMS (ESI$^+$, CH_3OH) m/z: $[M + Na]^+$ Calcd for $C_9H_{17}IO_2Na$ 307.0165; Found 307.0165.

2-((5-Iodopentyl)oxy)tetrahydro-2*H*-pyran, 5c. *New product*. *From pentane-1,5-diol*. A 100 mL round-bottom flask, was successively charged 20.90 mL (20.80 g, 199.71 mmol, 5.0 equiv.) of pentane-1,5-diol, 1.50 g (5.97 mmol, 15% in mole) of pyridinium *p*-toluenesulfonate (PPTS) and 3.62 ml (3.35 g, 40.00 mmol, 1.0 equiv.) of 3,4-dihydro-2*H*-pyran. The resulting mixture was stirred at ambient temperature for 72 h and poured on 150 mL of water. The resulting mixture was extracted with 50 mL of dichloromethane (x 3) and the combined organic layers were dried over $MgSO_4$ and concentrated to yield a colorless residue which was poured onto into a chromatographic column prepared with 200 g of silica and 70:30 diethyl ether/petroleum ether. The less polar 1,5-bis((tetrahydro-2*H*-pyran-2-yl)oxy)pentane (R_f = 0.9, diethyl ether/petroleum ether, 70:30),) eluted first (see the ^{1}H NMR spectrum in the SI), followed by 5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentan-1-ol which was obtained as a colorless oil (6.20 g, 82%). R_f = 0.3 (diethyl ether/petroleum ether, 70:30). ^{1}H NMR (C_6D_6, 300 MHz) δ = 4.57 (t, *J* = 6.5 Hz, 1 H), 3.85–3.76 (m, 2 H), 3.42–3.27 (m, 4 H), 1.82–1.68 (m, 1 H), 1.62–1.52 (m, 3 H), 1.44–1.18 (m, 8 H). ^{13}C{^{1}H} NMR (C_6D_6, 75 MHz) δ = 98.7 (t), 67.5 (s), 62.5 (s), 61.7 (s), 32.9 (s), 30.0 (s), 23.0 (s), 19.7 (s). IR (film, cm^{-1}): 868, 1021, 2865, 2937, 3404. HRMS (ESI$^+$, CH_3OH) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{20}O_3Na$ 211.1305; Found 211.1307. *Synthesis of iodide* **5c**. A 200-mL, one necked Schlenk tube, fitted with a magnetic stirring bar, and connected to an argon inlet tube was successively charged with 100 mL of dichloromethane, 5.0 g (26.50 mmol,

1.0 equiv.) of 5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentan-1-ol, 3.61 g (53.00 mmol, 2.0 equiv.) of imidazole, 9.05 g (34.50 mmol, 1.3 equiv.) of triphenylphosphine. The resulting solution was cooled to 0 °C, then, 9.43 g (37.15 mmol, 1.40 equiv.) of molecular iodine were added portion wise over a 20 minutes period. The resulting orange solution was warmed up to ambient temperature and stirring was continued for 2 hours before the addition of 100 mL of water containing 5.0 g of sodium sulfite. The biphasic system was vigorously stirred for 30 minutes and the organic phase was washed with 50 mL of water (x 3), dried over $MgSO_4$, and concentrated to yield a colorless solid which was taken-up in a mixture (100 mL) of petroleum ether and diethyl ether (75:25) until the precipitation of triphenylphosphine oxide which was removed by filtration over a sintered glass filter. The filtrate was concentrated to yield 11.2 g a colorless paste which was dissolved in 5 ml of diethyl ether and poured into a chromatographic column (30 × 2.5 cm, petroleum ether/diethyl ether 80:20) filled with 100 g of silica. The combined fractions were evaporated *in vacuo* at a temperature of 40 °C to afford 6.73 g (85%) of iodide **5c** as a yellowish oil. R_f = 0.6 (petroleum ether/diethyl ether, 80:20). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.58 (t, *J* = 2.9 Hz, 1 H), 3.91–3.83 (m, 1 H), 3.79–3.71 (m, 1 H), 3.54–3.43 (m, 1 H), 3.43–3.36 (m, 1 H), 3.20 (t, *J* = 6.8 Hz, 2 H), 2.86 (quint, *J* = 6.1 Hz, 2 H), 1.92–1.43 (m, 10 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ = 98.9 (t), 67.2 (t), 62.4 (s), 30.7 (s), 28.7 (s), 27.3 (s), 25.5 (s), 19.7 (s), 6.9 (s). IR (film, cm^{-1}): 868, 1030, 1118, 2865, 2937. HRMS [ESI$^+$, CH_3OH/CH_2Cl_2 (90:10)] m/z: $[M + Na]^+$ Calcd for $C_{10}H_{19}O_2INa$ 321.0322; Found 321.0320.

2-(Dibenzylamino)-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanenitrile, 6a. *Procedure A*. An oven-dried, one necked 200-mL Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube was flushed with argon and was successively charged with 20 mL of dry THF and 3.80 mL (2.73 g, 26.90 mmol, 1.35 equiv.) of diisopropylamine. The flask was then cooled to –80 °C (ethanol/liquid nitrogen bath) and 15.0 mL (24.00 mmol, 1.2 equiv.) of *n*-butyllithium (1.6 M in hexane) were slowly added to the previous solution. Stirring was continued for 30 min and the solution was stirred at 0 °C (ice bath) for an additional 30 minutes period at that temperature. The LDA solution was rapidly transferred (*via* a cannula) into a 200-mL Schlenk tube cooled to –80 °C containing 4.72 g (19.97 mmol, 1.0 equiv.) of *N,N*-dibenzylaminoacetonitrile (**4**) dissolved in 30 mL of dry THF. The solution turned rapidly deep red and was allowed to warm to –30 °C for 1.5 hours and cooled to –80 °C. Then, 5.90 g (21.84 mmol, 1.1 equiv.) of iodide **3a** were added to the anion solution and the reaction mixture was warmed to 0 °C over a 1.5 hours period. The reaction was quenched by the addition of 10 mL of ethanol and the solvents were evaporated under reduced pressure to afford a yellow paste which was poured into a mixture of diethyl ether (100 mL) and water (50 mL). The ethereal layer was separated, dried over $MgSO_4$ and concentrated to afford a yellow viscous oil (6.95 g) which was dissolved in 10 ml of a 50:50 mixture of petroleum ether and diethyl ether and poured

on a chromatography column (30 × 5.0 cm, petroleum ether/diethyl ether, 80:20) filled with 50 g of silica. The combined fractions were evaporated to afford 5.90 g (78%) of α-aminonitrile **6a** as a highly yellowish viscous oil. R_f = 0.5 (petroleum ether/diethyl ether, 7:3). ^{1}H NMR ($CDCl_3$, 400 MHz, 2 diastereoisomers) δ = 7.41–7.26 (m, 10 H), 4.43 (t, *J* = 2.05 Hz, 0.5 H), 4.42 (t, *J* = 2.05 Hz, 0.5 H), 3.98 (d, J_{AB} = 13.60 Hz, 2 H), 3.82–3.62 (m, 3 H), 3.45–3.42 (m, 1 H), 3.36 (d, J_{AB} = 13.60 Hz, 2 H), 3.35–3.25 (m, 1 H), 2.00–1.40 (m, 10 H). ^{13}C{^{1}H} NMR [$CDCl_3$, 100 MHz, 2 diastereoisomers, splitting signals are indicated with and asterisk (*)] δ = 137.8 (q), 128.73 (t), 128.72 (t), 127.5 (t), 117.5 (q), [98.83 (t), 98.78 (t)]*, [66.2 (s), 66.1 (s)]*, [62.3 (s), 62.2 (s)]*, [55.33 (s), 55.30 (s)]*, [52.6 (t), 52.5 (t)]*, [30.55 (s), 30.52 (s)]*, [28.3 (s), 28.2 (s)]*, 25.9 (s), [25.35 (s), 25.34 (s)]* [19.54 (s), 19.46 (s)]*. IR (film, cm^{-1}) 697, 1028, 1453, 2222, 2940. HRMS [ESI$^+$, CH_3CN/CH_3OH (90:10)] m/z: [M + Na]$^+$ Calcd for $C_{24}H_{30}N_2O_2Na$ 401.2199; Found 401.2197.

2-(Dibenzylamino)-6-((tetrahydro-2H-pyran-2-yl)oxy)hexanenitrile, 6b. The synthesis was as reported for **6a** but with 4.68 g (19.80 mmol, 1.0 equiv.) of α-aminonitrile **4** and 6.20 g (21.82 mmol, 1.1 equiv.) of iodide **5b** as the alkylating agent. The crude oily residue (8.30 g) was diluted in 10 mL of a mixture or petroleum ether and diethyl ether (50:50) and poured into a chromatographic (30 × 5.0 cm, petroleum ether/diethyl ether, 70:30) filled with 50 g of silica. The combined fractions were evaporated to afford 6.21 g (83%) of α-aminonitrile **6b** as a yellowish highly viscous oil. R_f = 0.50 (petroleum ether/diethyl ether, 70:30). ^{1}H NMR ($CDCl_3$, 400 MHz, 2 diastereoisomers) δ = 7.41–7.26 (m, 10 H), 4.58–4.56 (m, 1 H), 3.97 (d, J_{AB} = 13.60 Hz, 2 H), 3.90–3.80 (m, 1 H), 3.75–3.66 (m, 1 H), 3.60 (t, ^3J = 7.35 Hz, 1 H), 3.55–3.45 (m, 1 H), 3.39 (d, J_{AB} = 13.60 Hz, 2 H), 3.36–3.30 (m, 1 H), 2.00–1.77 (m, 3 H), 1.75–1.40 (m, 9 H). ^{13}C{^{1}H} NMR [$CDCl_3$, 100 MHz, 2 diastereoisomers, splitting signals are indicated with an asterisk (*)] δ = 137.8 (q), 128.7 (t), 128.5 (t), 127.5 (t), 117.5 (q), [98.75 (t), 98.72 (t)]*, 66.9 (s), 62.2 (s), 55.3 (s), [52.67 (t), 52.63 (t)]*, 31.1 (s), 30.7 (s), 28.8 (s), 25.4 (s), [22.69 (s), 22.67 (s)]*, 19.5 (s). IR (film, cm^{-1}) 697, 1028, 1453, 2223, 2939. HRMS (ESI$^+$, CH_3OH) m/z: [M + Na]$^+$ Calcd for $C_{25}H_{32}N_2O_2Na$ 415.2356; Found 415.2351.

2-(Dibenzylamino)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)heptanenitrile, 6c. *New product*. The synthesis was as reported for **6a** but with 2.00 g (8.46 mmol, 1.0 equiv.) of α-aminonitrile **4** and 2.77 g (9.30 mmol, 1.10 equiv.) of iodide **5c** as the alkylating agent. The crude oily residue was diluted in 10 mL of a mixture or petroleum ether and diethyl ether (50:50) and poured into a chromatographic (30 × 5.0 cm, petroleum ether/diethyl ether, 70:30) filled with 50 g of silica. The combined fractions were evaporated to afford 2.90 g (85%) of α-aminonitrile **6c** as a yellowish highly viscous oil. R_f = 0.60 (petroleum ether/diethyl ether, 7:3). ^{1}H NMR ($CDCl_3$, 300 MHz, 2 diastereoisomers) δ = 7.38–7.28 (m,

10 H), 4.55–4.52 (m, 1 H), 3.95 (d, *J* = 13.8 Hz, 2 H), 3.86–3.79 (m, 1 H), 3.72–3.63 (m, 1 H), 3.55 (t, *J* = 7.0 Hz, 1 H), 3.52–3.45 (m, 1 H), 3.37 (d, *J* = 13.8 Hz, 2 H), 3.36–3.25 (m, 1 H), 1.91–1.11 (m, 14 H). $^{13}C\{^1H\}$ NMR [$CDCl_3$, 75 MHz, 2 diastereoisomers, splitting signals are indicated with an asterisk (*)] δ = 137.9 (q), 128.7 (t), 128.5 (t), 127.5 (t), 117.6 (q), [98.9 (t), 98.8 (t)]*, [67.28 (s), 67.26 (s)]*, [62.38 (s), 62.36 (s)]*, 55.4 (s), 52.7 (t), 31.3 (s), 30.7 (s), 29.5 (s), [25.62 (s), 25.48 (s)]*, [19.70 (s), 19.68 (s)]*. IR (film, cm^{-1}): 698, 1026, 1119, 1454, 2225, 2939. HRMS (ESI^+, CH_3OH) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{34}N_2O_2Na$ 429.2512; Found 429.2516.

2-(dibenzylamino)pentanenitrile, 6d. *New product*. The synthesis of α-aminonitrile **6d** was carried out according to procedure A but with 6.00 g (25.39 mmol, 1.0 equiv.) of α-aminonitrile **4**, and 2.72 mL (4.74 g, 27.89 mmol, 1.10 equiv.) of iodopropane (**5d**). After work-up, the crude oily residue (6.72 g) which was poured on a chromatography column (30 × 5.0 cm, petroleum ether/diethyl ether, 80:20) filled with 100 g of silica. The combined fractions were evaporated to afford 5.36 g (76%) of α-aminonitrile **6d** as a highly yellowish viscous oil. R_f = 0.70 (petroleum ether/diethyl ether, 95:5). ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.38–7.28 (m, 10 H), 4.00 (d, *J* = 13.8 Hz, 2 H), 3.63 (t, *J* = 7.0 Hz, 1 H), 3.43 (d, *J* = 13.8 Hz, 2 H), 1.95–1.75 (m, 2 H), 1.40–1.60 (m, 2 H), 0.87 (t, *J* = 7.0 Hz, 3 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 138.0 (q), 128.8 (t), 128.6 (t), 127.6 (t), 117.7 (q), 55.4 (s), 52.5 (t), 33.4 (s), 19.1 (s), 13.2 (p). IR (film, cm^{-1}): 696, 1453, 2222, 2960, 3030. HRMS (ESI^+, CH_3OH) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{22}N_2Na$ 301.1675; Found 301.1674.

2-(Dibenzylamino)heptanenitrile, 6e. *New product*. The synthesis of α-aminonitrile **6e** was carried out according to procedure A, but with 2.0 g (8.46 mmol, 1.0 equiv.) of α-aminonitrile **4** and 1.21 mL (1.83 g, 9.27 mmol, 1.09 equiv.) of 1-iodopentane (**5e**) as the alkylating agent. The crude oily residue (2.66 g) was diluted with 5 mL of dichloromethane and poured into a chromatographic (30 × 2.5 cm, petroleum ether/diethyl ether, 95:5) filled with 60 g of silica. The combined fractions were evaporated to afford 2.10 g (81%) of α-aminonitrile **6e** as a yellowish viscous oil. R_f = 0.75 (petroleum ether/diethyl ether, 95:5). ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.42–7.28 (m, 10 H), 3.98 (d, *J* = 13.8 Hz, 2 H), 3.59 (t, *J* = 7.0 Hz, 1 H), 3.41 (d, *J* = 13.8 Hz, 2 H), 1.90–1.75 (m, 2 H), 1.55–1.38 (m, 2 H), 1.35–1.25 (m, 2 H), 1.21–1.13 (m, 2 H), 0.88 (t, *J* = 7.0 Hz, 3 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ = 138.0 (q), 128.8 (t), 128.5 (t), 127.5 (t), 117.7 (q), 55.4 (s), 52.7 (t), 31.3 (s), 30.9 (s), 25.4 (s), 22.4 (s), 13.9 (p). IR (film, cm^{-1}): 698, 1450, 2222, 2959, 3032. HRMS (ESI^+, CH_3OH) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{26}N_2Na$ 329.1994; Found 329.1987.

2-(Dibenzylamino)nonanenitrile, 6f. *New product*. The synthesis of α-aminonitrile **6f** was carried out according to procedure A, but with 3.0 g (12.70 mmol) of α-aminonitrile **4** and 2.29 mL (3.15 g, 13.97 mmol, 1.10 equiv.) of 1-iodoheptane (**5f**) as the alkylating agent. The crude oily residue (4.85 g) was diluted with the eluent mixture and poured into a chromatographic (30 × 2.5 cm, petroleum ether/diethyl ether, 95:5) filled with 60 g of silica. The combined fractions were evaporated to afford 3.39 g (80%) of α-aminonitrile **6f** as a highly yellowish viscous oil. R_f = 0.75 (petroleum ether/diethyl ether, 95:5). 1-iodoheptane in excess was visualized on the TLC plate with phosphomolybdic acid and was eluted in the first fractions. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.42–7.28 (m, 10 H), 3.98 (d, *J* = 13.8 Hz, 2 H), 3.60 (t, *J* = 7.0 Hz, 1 H), 3.41 (d, *J* = 13.8 Hz, 2 H), 1.90–1.75 (m, 2 H), 1.55–1.15 (m, 10 H), 0.92 (t, *J* = 7.0 Hz, 3 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ = 138.0 (q), 128.8 (t), 128.5 (t), 127.5 (t), 117.7 (q), 55.4 (s), 52.7 (t), 31.7 (s), 31.3 (s), 29.0 (s), 28.7 (s), 25.7 (s), 22.6 (s), 14.1 (p). IR (film, cm^{-1}): 695, 1452, 2221, 2960, 3035. HRMS (ESI^+, CH_3OH) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{30}N_2Na$ 357.2301; Found 357.2303.

2-(Dibenzylamino)tridecanenitrile, 6g. *New product*. The synthesis of α-aminonitrile **6g** was carried out according to procedure A, but with 1.0 g (4.23 mmol) of α-aminonitrile **4** and 1.07 mL (1.30 g, 4.62 mmol, 1.10 equiv.) of 1-iodoundecane (**5g**) as the alkylating agent. The crude oily residue (1.70 g) was diluted with the eluent mixture and poured into a chromatographic (30 × 4.7 cm, petroleum ether/diethyl ether, 98:2) filled with 70 g of silica. The combined fractions were evaporated to afford 1.29 g (78%) of α-aminonitrile **6g** as a yellowish highly viscous oil. R_f = 0.20 (petroleum ether/diethyl ether, 98:2). 1-Iodoundecane in excess was visualized on the TLC plate with phosphomolybdic acid and was eluted in the first fractions. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.42–7.28 (m, 10 H), 3.99 (d, *J* = 13.8 Hz, 2 H), 3.60 (t, *J* = 7.0 Hz, 1 H), 3.41 (d, *J* = 13.8 Hz, 2 H), 1.90–1.75 (m, 2 H), 1.53–1.15 (m, 18 H), 0.93 (t, *J* = 7.0 Hz, 3 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ = 138.0 (q), 128.8 (t), 128.5 (t), 127.5 (t), 117.7 (q), 55.4 (s), 52.7 (t), 31.9 (s), 31.3 (s), 29.5 (s), 29.35 (s), 29.33 (s), 28.7 (s), 25.7 (s), 22.7 (s), 29.6 (s), 14.1 (p). IR (film, cm^{-1}): 698, 1449, 2221, 3035. HRMS (ESI^+, CH_3OH) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{38}N_2Na$ 413.2927; Found 413.2919.

2-(Dibenzylamino)hexadecanenitrile, 6h. *New product*. The synthesis of α-aminonitrile **6h** was carried out according to procedure A, but with 1.50 g (6.35 mmol) of α-aminonitrile **4** and 1.64 g (5.05 mmol, 0.8 equiv.) of 1-iodotetradecane (**5h**) as the alkylating agent. The crude oily residue (2.70 g) was diluted with the eluent mixture and poured into a chromatographic (30 × 4.7 cm, petroleum ether/diethyl ether, 98:2) filled with 60 g of silica. The combined fractions were evaporated to afford 1.60 g (72%, based on 1-iodotetradecane) of α-aminonitrile **6h** as a highly yellowish viscous oil. R_f =

0.70 (petroleum ether/diethyl ether, 98:2). 1-Iodotetradecane in excess was visualized on the TLC plate with phosphomolybdic acid and was eluted in the first fractions. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.42–7.28 (m, 10 H), 3.99 (d, *J* = 13.8 Hz, 2 H), 3.60 (t, *J* = 7.0 Hz, 1 H), 3.41 (d, *J* = 13.8 Hz, 2 H), 1.90–1.75 (m, 2 H), 1.52–1.15 (m, 24 H), 0.93 (t, *J* = 7.0 Hz, 3 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ = 138.0 (q), 128.8 (t), 128.5 (t), 127.5 (t), 118.7 (q), 55.4 (s), 52.7 (t), 32.0 (s), 31.3 (s), 29.72 (s), 29.69 (s), 29.67 (s), 29.6 (s), 29.5 (s), 29.39 (s), 29.33 (s), 28.7 (s), 25.7 (s), 22.7 (s), 14.1 (p). IR (film, cm^{-1}): 698, 1449, 2221, 3035. HRMS (ESI^+, CH_3OH) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{44}N_2Na$ 455.3397; Found 455.3399.

***N*,*N*-Dibenzyl-1,7-bis((tetrahydro-2H-pyran-2-yl)oxy)heptan-4-amine, 8a.** *New product*. *Procedure B: step one, alkylation*. An oven dried, 200-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube was flushed with argon, and was successively charged with 10 mL of dry THF and 6.67 g (17.62 mmol, 1.00 equiv.) of α-aminonitrile **6a**. The flask was then cooled to –80 °C and 20 mL of a LDA solution in dry THF [prepared from 4.23 mL (3.03 g, 29.95 mmol, 1.70 equiv.) of diisopropylamine and 17.62 mL (28.19 mmol, 1.60 equiv.) of butyllithium (1.60 M solution in hexane)] were rapidly added *via* a canula. The anion solution turned rapidly yellow and was allowed to warm to –20 °C for 2 h and was then cooled to –80 °C. Then, 6.19 g (22.91 mmol, 1.30 equiv.) of 2-(3-iodopropoxy)tetrahydro-2*H*-pyran (**5a**) was added dropwise and the reaction mixture was allowed to warm to –20 °C for 3 h. The reaction was quenched by the addition of 10 mL of ethanol and the solvents were evaporated under reduced pressure to yield the corresponding quaternary α-aminonitrile **7a**, which was used in the next step without further purification. *Step two: reductive decyanation*. This oily residue was dissolved in 30 mL of ethanol and poured in a 100-mL, one-necked flask, equipped with a rubber septum. Then, 2.66 g of $NaBH_4$ (70.48 mmol, 4.0 equiv.) were added in portions. Stirring was continued for 12 h at room temperature, and 0.66 g of $NaBH_4$ (17.62 mmol, 1.0 equiv.) were added to the solution which was refluxed for 3 h. The solvents were evaporated under reduced pressure, and the crude material was taken-up with 20 mL of a 15% ammonia solution and the aqueous layer was extracted twice with 25 ml of diethyl ether. The combined organic layers were washed with 25 mL of water, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The crude oily residue (9.10 g) was diluted in 10 mL of a mixture or petroleum ether and diethyl ether (80:20) and poured into a chromatographic (30 × 5.0 cm, petroleum ether/diethyl ether, 70:30) filled with 70 g of silica. The combined fractions were evaporated to afford 7.63 g (87%) of amine **8a** as a colorless highly viscous oil. R_f = 0.35 (petroleum ether/diethyl ether, 80:20). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.37–7.17 (m, 10 H), 4.53–4.49 (m, 2 H), 3.93–3.78 (m, 2 H), 3.57 (s, 4 H), 3.74–3.41 (m, 4 H), 3.36–3.24 (m, 2 H), 2.45 (quint., *J* = 6.50 Hz, 1 H),

1.92–1.25 (m, 20 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 140.6 (q), 128.9 (t), 128.1 (t), 126.6 (t), 98.9 (t), 98.8 (t), 67.8 (s), 67.6 (s), 62.4 (s), 56.98 (t), 56.93 (t), 56.89 (t), 53.3 (s), 30.8 (s), 27.40 (s), 27.37 (s), 27.29 (s), 27.25 (s), 26.16 (s), 26.10 (s), 25.5 (s), 19.78 (s), 19.76 (s). IR (film, cm^{-1}) 1206, 1436, 1683, 1736, 3241. HRMS [ESI^+, CH_2Cl_2/CH_3OH (90:10)] m/z: $[M + Na]^+$ Calcd for $C_{31}H_{45}NO_4Na$ 518.3241; Found 518.3242.

***N*,*N*-Dibenzyl-1,8-bis((tetrahydro-2H-pyran-2-yl)oxy)octan-4-amine, 8b.** *New product*. The synthesis of amine **8b** was carried out according to procedure B, but with 6.10 g (16.11 mmol, 1.00 equiv.) of α-aminonitrile **6a** and 5.95 g (20.94 mmol, 1.30 equiv.) of 2-(4-iodobutoxy)tetrahydro-2*H*-pyran (**5b**) as the alkylating agent. The crude oily residue (8.10 g) was diluted in 10 mL of a mixture or petroleum ether and diethyl ether (80:20) and poured into a chromatographic (30 × 5.0 cm, petroleum ether/diethyl ether, 70:30) filled with 70 g of silica. The combined fractions were evaporated to afford 6.75 g (82%) of amine **8b** as a colorless highly viscous oil. R_f = 0.30 (petroleum ether/diethyl ether, 80:20). ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.37–7.20 (m, 10 H), 4.58–4.55 (m, 1 H), 4.51–4.50 (m, 1 H), 3.90–3.80 (m, 2 H), 3.56 (s, 4 H), 3.73–3.44 (m, 4 H), 3.36–3.24 (m, 2 H), 2.45 (quint., J = 6.50 Hz, 1 H), 1.88–1.22 (m, 22 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 140.6 (q), 128.9 (t), 128.1 (t), 126.6 (t), 98.9 (t), 98.8 (t), 98.77 (t), 98.75 (t), 67.8 (s), 67.6 (s), 67.55 (s), 67.49 (s), 62.4 (s), 62.2 (s), 57.07 (t), 57.01 (t), 53.3 (s), 30.8 (s), 29.93 (s), 29.87 (s), 29.36 (s), 29.33 (s), 27.40 (s), 27.36 (s), 26.30 (s), 26.25 (s), 26.18 (s), 25.5 (s), 23.95 (s), 23.91 (s), 23.89 (s), 23.86 (s), 19.7 (s), 19.6 (s). IR (film, cm^{-1}) 1206, 1436, 1683, 1736, 3241. HRMS [ESI^+, CH_2Cl_2/CH_3OH, (90:10)] m/z: $[M + Na]^+$ Calcd for $C_{32}H_{47}NO_4Na$ 532.3397; Found 532.3402.

***N*,*N*-Dibenzyl-1,9-bis((tetrahydro-2*H*-pyran-2-yl)oxy)nonan-4-amine, 8c.** *New product*. The synthesis of amine **8c** was carried out according to procedure B, but with 4.50 g (11.88 mmol, 1.00 equiv.) of α-aminonitrile **6a** and 4.60 g (15.45 mmol, 1.30 equiv.) of 2-(5-iodopentyl)oxy)tetrahydro-2*H*-pyran (**5c**) as the alkylating agent. The crude oily residue (**7c**, 7.5 g) was diluted in 10 mL of a mixture or petroleum ether and diethyl ether (80:20) and poured into a chromatographic (30 × 5.0 cm, petroleum ether/diethyl ether, 70:30) filled with 70 g of silica. The combined fractions were evaporated to afford 5.20 g (83%) of amine **8c** as a colorless highly viscous oil. R_f = 0.40 (petroleum ether/diethyl ether, 80:20). ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.37–7.20 (m, 10 H), 4.58–4.55 (m, 1 H), 4.53–4.50 (m, 1 H), 3.90–3.80 (m, 2 H), 3.60 (d, J_{AB} = 14.0 Hz, 2 H), 3.50 (d, J_{AB} = 14.0 Hz, 2 H), 3.73–3.44 (m, 4 H), 3.40–3.20 (m, 2 H), 2.44 (quint., J = 6.50 Hz, 1 H), 1.90–1.45 (m, 18 H), 1.43–1.14 (m, 6 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 140.7 (q), 128.9 (t), 128.0 (t), 126.6 (t), 98.9 (t), 98.8 (t), 67.8 (s), 67.6 (s), 62.4 (s), 62.3 (s), 56.98 (t), 56.91 (t), 53.3 (s), 30.8 (s), 29.8 (s), 29.3 (s), 27.4 (s), 27.2 (s),

27.13 (s), 27.09 (s), 26.4 (s), 26.3 (s), 25.5 (s), 19.77 (s), 19.75 (s), 19.71 (s). IR (film, cm^{-1}) 697, 1027, 1118, 1453, 2855, 2936. HRMS [ESI^+, CH_2Cl_2/CH_3OH, (90:10)] m/z: $[M + Na]^+$ Calcd for $C_{33}H_{49}NO_4Na$ 546.3554; Found 546.3553.

***N*,*N*-Dibenzyl-1-((tetrahydro-2*H*-pyran-2-yl)oxy)heptan-4-amine, 8d**. *New product*. The synthesis of amine **8d** was carried out according to procedure B, but with 2.0 g (5.28 mmol, 1.00 equiv.) of α-aminonitrile **6a** and 1.03 mL (1.80 g, 10.56 mmol, 2.0 equiv.) of 1-iodopropane as the alkylating agent. The crude oily residue (**8d**, 2.50 g) was diluted in 10 mL of a mixture or petroleum ether and diethyl ether (80:20) and poured into a chromatographic (30 × 3.0 cm, petroleum ether/diethyl ether, 70:30) filled with 40 g of silica. The combined fractions were evaporated to afford 1.62 g (76%) of amine **8d** as a yellowish highly viscous oil. R_f = 0.80 (petroleum ether/diethyl ether, 80:20). ^1H NMR ($CDCl_3$, 300 MHz, 2 diastereoisomers) δ = 7.42–7.22 (m, 10 H), 4.52–4.49 (m, 1 H), 3.91–3.80 (m, 1 H), 3.61 (d, J_{AB} = 13.60 Hz, 2 H), 3.59 (d, J_{AB} = 13.60 Hz, 2 H), 3.70–3.43 (m, 2 H), 3.32–3.22 (m, 1 H), 2.45 (quint., J = 6.50 Hz, 1 H), 1.87–1.14 (m, 14 H), 0.83 (t, J = 7.35 Hz, 3 H). $^{13}C\{^1H\}$ NMR [$CDCl_3$, 75 MHz, 2 diastereoisomers, splitting signals are indicated with an asterisk (*)] δ = 140.7 (q), 128.9 (t), 128.0 (t), 126.6 (t), [98.9 (t), 98.8 (t)]*, [67.8 (s), 67.6 (s)]*, [62.39 (s), 62.37 (s)]*, [56.78 (t), 56.73 (t)]*, 53.3 (s), 31.7 (s), 30.8 (s), [27.35 (s), 27.22 (s)]*, [26.42 (s), 26.36 (s)]*, 25.5 (s), [20.40 (s), 20.37 (s)], [19.76 (s), 19.74 (s)]*, [14.32 (p), 14.31 (p)]*. IR (film, cm^{-1}) 698, 1025, 1449, 1495, 2930. HRMS (ESI^+, CH_3OH) m/z: $[M + H]^+$ Calcd for $C_{26}H_{38}NO_2$ 396.2897; Found 396.2903.

***N*,*N*-Dibenzyl-8-((tetrahydro-2*H*-pyran-2-yl)oxy)octan-4-amine, 8e**. *New product*. The synthesis of amine **8e** was carried out according to procedure B, but with 4.10 g (10.44 mmol, 1.00 equiv.) of α-aminonitrile **6b** and 2.03 ml (3.55 g, 20.88 mmol, 2.0 equiv.) of 1-iodopropane as the alkylating agent. The crude oily residue (**8e**, 4.50 g) was diluted in 10 mL of a mixture or petroleum ether and diethyl ether (80:20) and poured into a chromatographic (30 × 5.0 cm, petroleum ether/diethyl ether, 70:30) filled with 50 g of silica. The combined fractions were evaporated to afford 3.37 g (76%) of amine **8e** as a yellowish highly viscous oil. R_f = 0.25 (petroleum ether/diethyl ether, 95:5). ^1H NMR ($CDCl_3$, 400 MHz, 2 diastereoisomers) δ = 7.42–7.22 (m, 10 H), 4.63–4.61 (m, 1 H), 3.95–3.90 (m, 1 H), 3.80–3.72 (m, 1 H), 3.62 (d, J_{AB} = 13.60 Hz, 2 H), 3.57 (d, J_{AB} = 13.60 Hz, 2 H), 3.60–3.52 (m, 1 H), 3.42–3.37 (m, 1 H), 2.49 (q, J = 6.50 Hz, 1 H), 1.90–1.20 (m, 16 H), 0.87 (t, J = 7.35 Hz, 3 H). $^{13}C\{^1H\}$ NMR [$CDCl_3$, 100 MHz, 2 diastereoisomers, splitting signals are indicated with an asterisk (*)] δ = 140.8 (q), 128.9 (t), 128.0 (t), 126.6 (t), [98.78 (t), 98.73 (t)]*, [67.6 (s), 67.5 (s)]*, 62.2 (s), [56.91 (t), 56.88 (t)]*, 53.4 (s), [31.92 (s), 31.87 (s)]*, 30.8 (s), [29.93 (s), 29.88 (s)]*, [29.70 (s), 29.65 (s)]*, 25.6 (s), [23.89 (s), 23.82

(s)]*, 20.4 (s), 19.6 (s), 14.3 (p). IR (film, cm^{-1}) 697, 1027, 1450, 1493, 2932. HRMS (ESI^+, CH_3OH) m/z: $[M + H]^+$ Calcd for $C_{27}H_{40}NO_2$ 410.3053; Found 410.3051.

***N*,*N*-Dibenzyl-9-((tetrahydro-2*H*-pyran-2-yl)oxy)nonan-4-amine, 8f.** *New product*. The synthesis of amine **8f** was carried out according to procedure B, but with 2.35 g (5.78 mmol, 1.00 equiv.) of α-aminonitrile **6c** and 1.12 ml (1.96 g, 11.56 mmol, 2.0 equiv.) of 1-iodopropane as the alkylating agent. The crude oily residue (**8f**, 3.10 g) was diluted in 10 mL of a mixture or petroleum ether and diethyl ether (80:20) and poured into a chromatographic (30 × 5.0 cm, petroleum ether/diethyl ether, 70:30) filled with 50 g of silica. The combined fractions were evaporated to afford 2.02 g (82%) of amine **8f** as a yellowish highly viscous oil. R_f = 0.40 (petroleum ether/diethyl ether, 95:5). ^1H NMR ($CDCl_3$, 300 MHz, 2 diastereoisomers) δ = 7.42–7.22 (m, 10 H), 4.60–4.57 (m, 1 H), 3.90–3.84 (m, 1 H), 3.75–3.66 (m, 1 H), 3.54 (s, 4 H), 3.52–3.47 (m, 1 H), 3.39–3.31 (m, 1 H), 2.42 (q, *J* = 6.50 Hz, 1 H), 1.90–1.20 (m, 18 H), 0.81 (t, *J* = 7.35 Hz, 3 H). $^{13}C\{^1H\}$ NMR [$CDCl_3$, 75 MHz, 2 diastereoisomers, splitting signals are indicated with an asterisk (*)] δ = 140.8 (q), 128.9 (t), 128.0 (t), 126.6 (t), [98.85 (t), 98.83 (t)]*, [67.69 (s), 67.66 (s)]*, 62.3 (s), 56.8 (t), 53.3 (s), [32.03 (s), 32.01 (s)]*, 30.8 (s), [29.82 (s), 29.79 (s)]*, 29.6 (s), [27.06 (s), 27.04 (s)]*, 26.4 (s), 25.5 (s), 20.4 (s), 19.7 (s), 14.3 (p). IR (film, cm^{-1}) 697, 744, 1027, 1453, 2856, 2931. HRMS [ESI^+, CH_3OH/CH_2Cl_2 (90:10)] m/z: $[M + H]^+$ Calcd for $C_{28}H_{42}NO_2$ 424.3210; Found 424.3206.

1,7-bis((Tetrahydro-2*H*-pyran-2-yl)oxy)heptan-4-amine, 9a. *New product*. <u>*Procedure C*</u>. A 300-mL stainless steel high-pressure hydrogenator was charged with 30 mL of ethanol, 10 mL of methanol, 0.50 g (6.5% in mass) of 20% $Pd(OH)_2/C$ and 7.60 g (15.33 mmol) of amine **8a**. Air was removed from the reactor by alternatively filling it with hydrogen and venting it three times. The hydrogen pressure (3.75×10^3 Torr, 5 bars) was applied, and the suspension was stirred for 72 h and heated at 60 °C on a stirring plate. The resulting clear solution was filtered over a small pad of Celite® and the vessel was washed with ethanol. The filtrate was concentrated under reduced pressure, to afford 4.80 g (99%) of amine **9a** which was utilized in the next step without purification. Highly viscous oil. R_f = 0.2 (dichloromethane/methanol, 90:10). ^1H NMR ($CDCl_3$, 300 MHz) δ = 4.59–4.57 (m, 2 H), 3.90–3.83 (m, 2 H), 3.79–3.71 (m, 2 H), 3.54–3.51 (m, 2 H), 3.44–3.37 (m, 2 H), 2.81–2.73 (m, 1 H), 1.89–1.21 (m, 20 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 98.90 (t), 98.88 (t), 67.7 (s), 62.4 (s), 51.0 (t), 34.7 (s), 30.8 (s), 26.5 (s), 26.4 (s), 25.5 (s), 24.0 (s), 19.7 (s). IR (film, cm^{-1}) 812, 1021, 1200, 2867, 3368. HRMS [ESI^+, CH_3OH/CH_2Cl_2 (90:10)] m/z: $[M + H]^+$ Calcd for $C_{17}H_{34}NO_4$ 316.2482; Found 316.2484.

1,8-bis((Tetrahydro-2*H*-pyran-2-yl)oxy)octan-4-amine, 9b. *New product*. The synthesis of amine **9b** has been carried out according to procedure C, but with 30 mL of ethanol and 10 mL of methanol, 0.5 g (7.5% in mass) of 20% $Pd(OH)_2/C$ and 6.70 g (13.14 mmol) of amine **8b**. The suspension was stirred for 72 h at 60 °C and the filtrate was concentrated under reduced pressure, to afford amine **9b** (4.33 g, 94%) which was utilized in the next step without purification. R_f = 0.2 (dichloromethane/methanol, 90:10). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.59–4.56 (m, 2 H), 3.91–3.82 (m, 2 H), 3.79–3.70 (m, 2 H), 3.54–3.47 (m, 2 H), 3.43–3.37 (m, 2 H), 2.78–2.71 (m, 1 H), 1.87–1.21 (m, 24 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 98.94 (t), 98.92 (t), 98.90 (t), 98.87 (t), 67.69 (s), 67.67 (s), 67.53 (s), 62.40 (s), 62.38 (s), 51.05 (t), 51.02 (t), 37.8 (s), 34.6 (s), 30.78 (s), 30.76 (s), 29.9 (s), 26.45 (s), 26.39 (s), 25.48 (s), 22.88 (s), 22.85 (s), 19.73 (s), 19.68 (s). IR (film, cm^{-1}) 1021, 1134, 1350, 2865, 2936. HRMS [ESI^+, CH_3OH/CH_2Cl_2 (90:10)] m/z: $[M + H]^+$ Calcd for $C_{18}H_{36}NO_4$ 330.2639; Found 330.2640.

1,9-bis((Tetrahydro-2*H*-pyran-2-yl)oxy)nonan-4-amine, 9c. *New product*. The synthesis of amine **9c** has been carried out according to procedure C, but with 30 mL of ethanol and 10 mL of methanol, 0.25 g (5% in mass) of 20% $Pd(OH)_2/C$ and 4.80 g (9.16 mmol) of amine **8c**. The suspension was stirred for 72 h at 60 °C and the filtrate was concentrated under reduced pressure, to afford amine **9c** (3.10 g, 98%) which was utilized in the next step without purification. R_f = 0.2 (dichloromethane/methanol, 90:10). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.59–4.56 (m, 2 H), 3.91–3.82 (m, 2 H), 3.79–3.70 (m, 2 H), 3.54–3.47 (m, 2 H), 3.44–3.35 (m, 2 H), 2.78–2.71 (m, 1 H), 1.87–1.21 (m, 26 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 98.87 (t), 67.69 (s), 67.66 (s), 67.57 (s), 62.4 (s), 51.07 (t), 51.04 (t), 37.9 (s), 34.6 (s), 30.78 (s), 30.75 (s), 26.44 (s), 26.38 (s), 26.0 (s), 25.49 (s), 25.48 (s), 19.71 (s), 19.67 (s). IR (film, cm^{-1}) 1021, 1134, 1200, 1440, 2934. HRMS [ESI^+, CH_3OH/CH_2Cl_2 (90:10)] m/z: $[M + H]^+$ Calcd for $C_{19}H_{38}NO_4$ 344.2795; Found 344.2794.

1-((Tetrahydro-2*H*-pyran-2-yl)oxy)heptan-4-amine, 9d. *New product*. The synthesis of amine **9d** has been carried out according to procedure C, but with 5 mL of ethanol and 10 mL of methanol, 0.14 g (10% in mass) of 20% $Pd(OH)_2/C$ and 1.43 g (3.61 mmol) of amine **8d**. The suspension was stirred for 72 h at 60 °C and the filtrate was concentrated under reduced pressure at a temperature lower than 50 °C, to afford amine **9d** (0.65 g, 84%) which was utilized in the next step without purification. R_f = 0.2 (dichloromethane/methanol, 90:10). ^{1}H NMR ($CDCl_3$, 300 MHz, 2 diastereoisomers) δ = 4.59–4.56 (m, 2 H), 3.91–3.83 (m, 2 H), 3.79–3.71 (m, 2 H), 3.54–3.47 (m, 2 H), 3.44–3.37 (m, 2 H), 2.79–2.71 (m, 1 H), 1.90–1.22 (m, 16 H), 0.92 (t, J = 6.70 Hz, 3 H). $^{13}C\{^1H\}$ NMR [$CDCl_3$, 75 MHz, 2 diastereoisomers, splitting signals are indicated with an asterisk (*)] δ = [98.87 (t), 98.84 (t)]*, [67.71 (s), 67.68 (s)]*, 62.3 (s), [50.82 (t), 50.79 (t)]*, 40.2 (s), 34.7 (s), 30.8 (s), [26.45 (s), 26.40 (s)]*, 25.5

(s), [19.7 (s), 19.3 (s)]*, 14.2 (p). IR (film, cm^{-1}) 1021, 1134, 1201, 1435, 2935. HRMS (ESI^+, CH_3OH) m/z: $[M + H]^+$ Calcd for $C_{12}H_{26}NO_2$ 216.1958; Found 216.1959.

8-((Tetrahydro-2*H*-pyran-2-yl)oxy)octan-4-amine, 9e. *New product*. The synthesis of amine **9e** has been carried out according to procedure C, but with 20 mL of ethanol and 10 mL of methanol, 0.25 g (8% in mass) of 20% $Pd(OH)_2/C$ and 3.00 g (7.32 mmol) of amine **8e**. The suspension was stirred for 48 h at 60 °C and the filtrate was concentrated under reduced pressure at a temperature lower than 50 °C, to afford amine **9e** (1.65 g, 98%) which was utilized in the next step without purification. R_f = 0.3 (dichloromethane/methanol, 90:10). ^1H NMR ($CDCl_3$, 400 MHz, 2 diastereoisomers) δ = 4.56–4.54 (m, 1 H), 3.90–3.80 (m, 1 H), 3.77–3.70 (m, 1 H), 3.52–3.45 (m, 1 H), 3.40–3.35 (m, 1 H), 2.75–2.65 (m, 1 H), 1.85–1.15 (m, 18 H), 0.89 (t, J = 6.70 Hz, 3 H). $^{13}C\{^1H\}$ NMR [$CDCl_3$, 100 MHz, 2 diastereoisomers, splitting signals are indicated with an asterisk (*)] δ = 98.9 (t), 67.5 (s), [62.34 (s), 62.32 (s)]*, 50.8 (t), 40.2 (s), [37.80 (s), 37.77 (s)]*, 30.7 (s), 29.8 (s), 25.5 (s), [22.83 (s), 22.80 (s)]*, 19.7 (s), 19.2 (s), 14.1 (p). IR (film, cm^{-1}) 813, 1021, 1118, 1454, 2931. HRMS (ESI^+, CH_3OH) m/z: $[M + H]^+$ Calcd for $C_{13}H_{28}NO_2$ 230.2114; Found 230.2117. Spectral data of amine **9e** were not reported in ref.[29]

9-((Tetrahydro-2*H*-pyran-2-yl)oxy)nonan-4-amine, 9f. *New product*. The synthesis of amine **9f** has been carried out according to procedure C, but with 25 mL of ethanol and 10 mL of methanol, 0.11 g (6% in mass) of 20% $Pd(OH)_2/C$ and 1.94 g (4.58 mmol) of amine **8f**. The suspension was stirred for 48 h at 60 °C and the filtrate was concentrated under reduced pressure at a temperature lower than 50 °C, to afford amine **9f** (1.09 g, 98%) which was utilized in the next step without purification. R_f = 0.3 (dichloromethane/methanol, 90:10). ^1H NMR ($CDCl_3$, 300 MHz, 2 diastereoisomers) δ = 4.56–4.54 (m, 1 H), 3.91–3.83 (m, 1 H), 3.77–3.70 (m, 1 H), 3.54–3.46 (m, 1 H), 3.43–3.35 (m, 1 H), 2.75–2.65 (m, 1 H), 1.85–1.15 (m, 20 H), 0.89 (t, J = 6.65 Hz, 3 H). $^{13}C\{^1H\}$ NMR [$CDCl_3$, 75 MHz, 2 diastereoisomers, splitting signals are indicated with an asterisk (*)] δ = 98.9 (t), [67.60 (s), 67.59 (s)]*, [62.38 (s), 62.37 (s)]*, 50.9 (t), 40.4 (s), 38.1 (s), 30.8 (s), [29.77 (s), 29.76 (s)]*, [26.47 (s), 26.45 (s)]*, 26.0 (s), 25.5 (s), 19.7 (s), 19.3 (s), 14.2 (p). IR (film, cm^{-1}) 814, 1022, 1119, 2858, 2928. HRMS [ESI^+, CH_3OH/CH_2Cl_2 (90:10)] m/z: $[M + H]^+$ Calcd for $C_{14}H_{30}NO_2$ 244.2271; Found 244.2268.

***tert*-Butyl (1,7-bis((tetrahydro-2*H*-pyran-2-yl)oxy)heptan-4-yl)carbamate, 10a**. *New product.* *Procedure D*. A round bottom 100 mL flask was charged 4.80 g (15.21 mmol, 1.0 equiv.) of amine **9a**, 15 mL of dichloromethane and 3.32 g (15.21 mmol, 1.0 equiv.) of Boc_2O and the resulting solution was stirred for 12 h at rt. The solvent was evaporated in vacuo to yield an oily residue (6.50 g) which

was poured into a chromatographic column (30 × 2.5 cm, petroleum ether/diethyl ether, 50:50) filled with 30 g of silica. The combined fractions were evaporated to afford 6.18 g (97%) of carbamate **10a** as a colorless highly viscous oil which solidified upon cooling. R_f = 0.4 (petroleum ether/diethyl ether, 50:50). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.59–4.56 (m, 2 H), 4.52–4.45 (m, 1 H), 3.90–3.80 (m, 2 H), 3.79–3.71 (m, 2 H), 3.66–3.54 (m, 1 H), 3.56–3.45 (m, 2 H), 3.44–3.36 (m, 2 H), 1.43 (s, 9 H), 1.89–1.36 (m, 20 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ = 155.7 (q), 98.96 (t), 98.86 (t), 78.8 (q), 67.4 (s), 62.46 (s), 62.38 (s), 50.4 (t), 32.1 (s), 30.75 (s), 30.72 (s), 28.4 (p), 26.15 (s), 26.11 (s), 25.4 (s), 19.74 (s), 19.69 (s). IR (film, cm^{-1}) 1206, 1364, 1697, 2869, 2940, 3342. HRMS [ESI$^+$, CH_2Cl_2/CH_3OH (90:10)] m/z: [M + Na]$^+$) Calcd for $C_{22}H_{41}NO_6Na$ 438.2826; Found 438.2830.

***tert*-Butyl (1,8-bis((tetrahydro-2*H*-pyran-2-yl)oxy)octan-4-yl)carbamate, 10b**. *New product.* Carbamate **10b** was synthesized according to procedure D but with 4.06 g (12.32 mmol, 1.0 equiv.) of amine **9b**, and 2.69 g (12.32 mmol, 1.0 equiv.) of Boc_2O. The solvent was evaporated in vacuo to yield an oily residue (5.3 g) which was poured into a chromatographic column (30 × 2.5 cm, petroleum ether/diethyl ether, 50:50) filled with 30 g of silica. The combined fractions were evaporated to afford 4.85 g (92%) of carbamate **10b** as a colorless highly viscous oil. R_f = 0.4 (petroleum ether/diethyl ether, 50:50). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.58–4.56 (m, 2 H), 4.40–4.35 (m, 1 H), 3.89–3.83 (m, 2 H), 3.77–3.69 (m, 2 H), 3.53–3.46 (m, 3 H), 3.44–3.33 (m, 2 H), 1.43 (s, 9 H), 1.38–1.83 (m, 22 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ = 155.7 (q), 98.98 (t), 98.89 (t), 98.83 (t), 78.8 (q), 67.44 (s), 67.40 (s), 62.46 (s), 62.37 (s), 62.32 (s), 50.5 (t), 35.4 (s), 32.1 (s), 30.7 (s), 29.68 (s), 29.65 (s), 28.4 (p), 26.16 (s), 26.12 (s), 25.50 (s), 25.48 (s), 22.68 (s), 22.64 (s), 19.75 (s), 19.70 (s), 19.66 (s). IR (film, cm^{-1}) 1206, 1436, 1683, 1736, 3241. HRMS [ESI$^+$, CH_2Cl_2/CH_3OH, (90:10)] m/z: [M + Na]$^+$ Calcd for $C_{23}H_{43}NO_6Na$ 452.2983; Found 452.2987.

***tert*-Butyl (1,9-bis((tetrahydro-2*H*-pyran-2-yl)oxy)nonan-4-yl)carbamate, 10c**. *New product.* Carbamate **10c** was synthesized according to procedure D but with 2.91 g (8.47 mmol, 1.0 equiv.) of amine **9c**, and 1.85 g (8.47 mmol, 1.0 equiv.) of Boc_2O. The solvent was evaporated in vacuo to yield an oily residue (3.8 g) which was poured into a chromatographic column (30 × 2.5 cm, petroleum ether/diethyl ether, 50:50) filled with 30 g of silica. The combined fractions were evaporated to afford 4.85 g (92%) of carbamate **10c** as a colorless highly viscous oil. R_f = 0.5 (petroleum ether/diethyl ether, 50:50. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.58–4.56 (m, 2 H), 4.40–4.35 (m, 1 H), 3.90–3.83 (m, 2 H), 3.78–3.69 (m, 2 H), 3.60–3.45 (m, 3 H), 3.43–3.34 (m, 2 H), 1.44 (s, 9 H), 1.90–1.30 (m, 24 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ = 155.7 (q), 99.0 (t), 98.9 (t), 78.8 (q), 67.5 (s), 67.4 (s), 62.47 (s), 62.39 (s), 50.5 (t), 35.6 (s), 32.1 (s), 30.78 (s), 30.76 (s), 30.72 (s), 29.7 (s), 28.4 (p), 26.2 (s),

26.1 (s), 25.7 (s), 25.49 (s), 25.46 (s), 19.75 (s), 19.71 (s), 19.69 (s). IR (film, cm^{-1}) 1021, 1170, 1696, 1712, 3341. HRMS [ESI^+, CH_2Cl_2/CH_3OH (90:10)] m/z: $[M + Na]^+$ Calcd for $C_{24}H_{45}NO_6Na$ 466.3139; Found 466.3143.

***tert*-Butyl (1-((tetrahydro-2*H*-pyran-2-yl)oxy)heptan-4-yl)carbamate, 10d.** *New product.* Carbamate **10d** was synthesized according to procedure D but with 1.30 g (6.03 mmol, 1.0 equiv.) of amine **9d**, 1.31 g (6.03 mmol, 1.0 equiv.) of Boc_2O. The solvents were evaporated in vacuo to yield an oily residue (2.0 g) which was poured into a chromatographic column (30 × 2.5 cm, petroleum ether/diethyl ether, 70:30) filled with 30 g of silica. The combined fractions were evaporated to afford 1.60 g (84%) of carbamate **10d** as a yellowish highly viscous oil. R_f = 0.4 (petroleum ether/diethyl ether, 70:30). ^1H NMR ($CDCl_3$, 400 MHz, 2 diastereoisomers) δ = 4.58–4.55 (m, 1 H), 4.45–4.35 (m, 1 H, br.), 3.89–3.82 (m, 1 H), 3.78–3.70 (m, 1 H), 3.60–3.52 (m, 1 H, br.), 3.53–3.46 (m, 1 H), 3.44–3.36 (m, 1 H), 1.44 (s, 9 H), 1.84–1.33 (m, 14 H), 0.91 (t, J = 6.80 Hz, 3 H). $^{13}C\{^1H\}$ NMR [$CDCl_3$, 100 MHz, 2 diastereoisomers, splitting signals are indicated with an asterisk (*)] δ = 155.7 (q), [99.0 (t), 98.9 (t)]*, 78.8 (q), 67.5 (s), [62.46 (s), 62.38 (s)]*, 50.3 (t), 37.9 (s), 32.1 (s), [30.8 (s), 30.7 (s)]*, 28.4 (p), [26.15 (s), 26.10 (s)]*, 25.5 (s), [19.74 (s), 19.70 (s)]*, 19.1 (s), 14.0 (p). IR (film, cm^{-1}) 868, 1170, 1519, 1692, 2869, 2936, 3345. HRMS (ESI^+, CH_3OH) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{33}NO_4Na$ 338.2302; Found 338.2298.

***tert*-Butyl (8-((tetrahydro-2*H*-pyran-2-yl)oxy)octan-4-yl)carbamate, 10e.** *New product.* Carbamate **10e** was synthesized according to procedure D but with 1.70 g (7.41 mmol) of amine **9e**, 1.61 g (7.41 mmol, 1.0 equiv.) of Boc_2O. The solvents were evaporated in vacuo to yield an oily residue (2.5 g) which was poured into a chromatographic column (30 × 2.5 cm, petroleum ether/diethyl ether, 60:40) filled with 30 g of silica. The combined fractions were evaporated to afford 2.30 g (94%) of carbamate **10e** as a yellowish highly viscous oil. R_f = 0.7 (petroleum ether/diethyl ether, 60:40). ^1H NMR ($CDCl_3$, 400 MHz, 2 diastereoisomers) δ = 4.57–4.54 (m, 1 H), 4.28 (d, J = 8.0 Hz, 1 H, br.), 3.90–3.82 (m, 1 H), 3.75–3.67 (m, 1 H), 3.60–3.52 (m, 1 H, br.), 3.51–3.46 (m, 1 H), 3.40–3.34 (m, 1 H), 1.42 (s, 9 H), 1.85–1.25 (m, 16 H), 0.91 (t, J = 6.80 Hz, 3 H). $^{13}C\{^1H\}$ NMR [$CDCl_3$, 100 MHz, 2 diastereoisomers, splitting signals are indicated with an asterisk (*)] δ = 155.7 (q), [98.82 (t), 98.77 (t)]*, 78.7 (q), [67.41 (s), 67.37 (s)]*, [62.29 (s), 62.24 (s)]*, 50.4 (t), 37.8 (s), [35.4 (s), 35.3 (s)]*, 30.7 (s), [29.66 (s), 29.63 (s)]*, 28.4 (p), 25.5 (s), [22.62 (s), 22.59 (s)]*, [19.64 (s), 19.61 (s)]*, 19.1 (s), 14.0 (p). IR (film, cm^{-1}) 868, 1170, 1519, 1692, 2869, 2936, 3345. HRMS (ESI^+, CH_3OH) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{35}NO_4Na$ 352.2458; Found 352.2457.

***tert*-Butyl (9-((tetrahydro-2*H*-pyran-2-yl)oxy)nonan-4-yl)carbamate, 10f.** *New product.* Carbamate **10f** was synthesized according to procedure D but with 1.40 g (5.75 mmol) of amine **9f**, 1.25 g (5.75 mmol, 1.0 equiv.) of Boc_2O. The solvents were evaporated in vacuo to yield an oily residue (2.0 g) which was poured into a chromatographic column (30 × 2.5 cm, petroleum ether/diethyl ether, 60:40) filled with 30 g of silica. The combined fractions were evaporated to afford 1.79 g (90%) of carbamate **10f** as a yellowish highly viscous oil. R_f = 0.40 (petroleum ether/diethyl ether, 80:20). ^{1}H NMR ($CDCl_3$, 300 MHz, 2 diastereoisomers) δ = 4.58–4.56 (m, 1 H), 4.24 (d, *J* = 8.0 Hz, 1 H, br.), 3.90–3.83 (m, 1 H), 3.77–3.69 (m, 1 H), 3.61–3.45 (m, 2 H), 3.41–3.34 (m, 1 H), 1.44 (s, 9 H), 1.89–1.23 (m, 18 H), 0.91 (t, *J* = 6.80 Hz, 3 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, 2 diastereoisomers) δ = 155.7 (q), 98.9 (t), 78.8 (q), 67.6 (s), 62.4 (s), 50.4 (t), 37.8 (s), 35.6 (s), 30.8 (s), 29.7 (s), 28.5 (s), 28.4 (p), 27.4 (s), 26.3 (s), 25.7 (s), 25.5 (s), 19.7 (s), 19.1 (s), 14.0 (p). IR (film, cm^{-1}) 868, 1170, 1519, 1692, 2869, 2936, 3345. HRMS (ESI$^+$, CH_3OH) m/z: [M + Na]$^+$ Calcd for $C_{19}H_{37}NO_4Na$ 366.2615; Found 366.2618.

***tert*-Butyl (1,7-dihydroxyheptan-4-yl)carbamate, 11a.** *New product.* <u>*Procedure E.*</u> A 200-mL, one necked Schlenk tube, fitted with a magnetic stirring bar, and connected to an argon inlet tube was successively charged with 25 mL of methanol, 6.10 g (14.67 mmol) of carbamate **10a**, and 0.74 g (2.93 mmol, 20% in mole) of pyridinium *p*-toluenesulfonate (PPTS). The reaction mixture was heated in a sand bath at 50 °C overnight. The solvent was removed under reduced pressure, and the crude material was stirred for 15 minutes in a biphasic mixture of diethyl ether (100 mL) and water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated to yield an oily residue (3.50 g) which was poured into a chromatographic column (30 × 2.5 cm, dichloromethane/methanol, 90:10) filled with 20 g of silica. The combined fractions were evaporated to afford 3.32 g (88%) of carbamate **11a**. R_f = 0.35 (dichloromethane/methanol, 90:10. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.45 (d, *J* = 7.0 Hz, 1 H), 3.67–3.64 (m, 5 H), 2.09 (s, 2 H, br.), 1.68–1.50 (m, 8 H), 1.44 (s, 9 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ = 156.3 (q), 79.1 (q), 62.1 (s), 50.1 (t), 31.9 (s), 28.8 (s), 28.4 (p). IR (film, cm^{-1}) 1170, 1364, 1531, 1674, 2932, 3311, 3404. HRMS [ESI$^+$, CH_2Cl_2/CH_3OH, (90:10)] m/z: [M + Na]$^+$ Calcd for $C_{12}H_{25}NO_4Na$ 270.1676; Found 270.1678.

***tert*-Butyl (1,8-dihydroxyoctan-4-yl)carbamate, 11b.** Carbamate **11b** was synthesized according to procedure E but with 4.74 g (11.03 mmol) of carbamate **10b**, and 0.55 g (2.18 mmol, 20% in mole) of pyridinium *p*-toluenesulfonate (PPTS). The organic layer was dried over $MgSO_4$ and concentrated to yield an oily residue (2.90 g) which was poured into a chromatographic column (30 × 2.5 cm, dichloromethane/methanol, 90:10) filled with 20 g of silica. The combined fractions were evaporated to afford 2.62 g (90%) of carbamate **11b**. R_f = 0.6 (dichloromethane/methanol, 90:10). ^{1}H NMR

($CDCl_3$, 300 MHz) δ = 4.45 (d, *J* = 7.0 Hz, 1 H), 3.67–3.64 (m, 5 H), 2.00–1075 (s, 2 H, br.), 1.44 (s, 9 H), 1.70–1.40 (m, 10 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 156.2 (q), 79.2 (q), 62.5 (s), 50.2 (t), 35.4 (s), 32.4 (s), 32.1 (s), 28.8 (s), 28.4 (p), 22.1 (s). IR (film, cm^{-1}) 1167, 1364, 1529, 1681, 2863, 2934, 3328. HRMS [ESI^+, CH_2Cl_2/CH_3OH (90:10)] m/z: $[M + Na]^+$ Calcd for $C_{13}H_{27}NO_4Na$ 284.1832; Found 284.1836. These spectral data ($^{13}C\{^1H\}$ NMR) did not match those reported in ref.[11b]

***tert*-Butyl (1,9-dihydroxynonan-4-yl)carbamate, 11c.** *New product.* Carbamate **11c** was synthesized according to procedure E but with 3.40 g (7.66 mmol) of carbamate **10c**, and 0.38 g (1.51 mmol, 20% in mole) of pyridinium *p*-toluenesulfonate (PPTS). The organic layer was dried over $MgSO_4$ and concentrated to yield an oily residue (2.90 g) which was poured into a chromatographic column (30 × 2.5 cm, dichloromethane/methanol, 90:10) filled with 20 g of silica. The combined fractions were evaporated to afford 1.85 g (87%) of carbamate **11c**. R_f = 0.2 (dichloromethane/methanol, 95:5. ^1H NMR ($CDCl_3$, 300 MHz) δ = 4.45 (d, *J* = 7.0 Hz, 1 H), 3.67–3.64 (m, 5 H), 2.60–2.40 (s, 2 H, br.), 1.44 (s, 9 H), 1.65–1.30 (m, 12 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 156.2 (q), 79.2 (q), 62.42 (s), 62.37 (s), 50.1 (t), 35.7 (s), 32.5 (s), 32.1 (s), 28.9 (s), 28.4 (p), 25.43 (s), 25.38 (s). IR (film, cm^{-1}) 1167, 1364, 1530, 1681, 2859, 2932, 3318. HRMS [ESI^+, CH_2Cl_2/CH_3OH (90:10)] m/z: $[M + Na]^+$ Calcd for $C_{14}H_{29}NO_4Na$ 298.1989; Found 298.1991.

***tert*-Butyl (1-hydroxyoctan-4-yl)carbamate, 11d.** *New product.* Carbamate **11d** was synthesized according to procedure E but with 1.40 g (4.44 mmol) of carbamate **10d**, and 0.28 g (1.11 mmol, 25% in mole) of pyridinium *p*-toluenesulfonate (PPTS). The organic layer was dried over $MgSO_4$ and concentrated to yield an oily residue (1.10 g) which was poured into a chromatographic column (30 × 2.5 cm, diethyl ether) filled with 20 g of silica. The combined fractions were evaporated to afford 0.97 g (94%) of carbamate **11d**. Colorless solid. M.p. = 86–88 °C. R_f = 0.45 (diethyl ether/petroleum ether, 80:20. ^1H NMR ($CDCl_3$, 300 MHz) δ = 4.28 (s, 1 H, br.), 3.66 (t, *J* = 6.5 Hz, 2 H), 3.60–3.55 (s, 1 H, br.), 1.76–1.71 (s, 1 H, br.), 1.65–1.30 (m, 8 H), 1.44 (s, 9 H), 0.91 (t, *J* = 7.50 Hz, 3 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 155.6 (q), 79.1 (q), 62.8 (s), 50.1 (t), 37.9 (s), 32.3 (s), 28.9 (s), 28.4 (p), 19.1 (s), 14.0 (p). IR (film, cm^{-1}) 1169, 1365, 1530, 1680, 2932, 3330. HRMS (ESI^+, CH_3OH) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{25}NO_3Na$ 254.1727; Found 254.1727.

***tert*-Butyl (1-hydroxynonan-5-yl)carbamate, 11e**. Carbamate **11e** was synthesized according to procedure E but with 3.25 g (9.86 mmol) of carbamate **10e**, and 0.50 g (1.97 mmol, 20% in mole) of pyridinium *p*-toluenesulfonate (PPTS). The organic layer was dried over $MgSO_4$ and concentrated to yield an oily residue (2.30 g) which was poured into a chromatographic column (30 × 2.5 cm, diethyl

ether) filled with 20 g of silica. The combined fractions were evaporated to afford 2.00 g (83%) of carbamate **11e**. Colorless highly viscous oil. R_f = 0.40 (diethyl ether/petroleum ether, 80:20). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.28 (d, *J* = 8.0 Hz, 1 H, br.), 3.65 (t, *J* = 6.5 Hz, 2 H), 3.60–3.55 (s, 1 H, br.), 1.72–1.68 (s, 1 H, br.), 1.65–1.30 (m, 10 H), 1.45 (s, 9 H), 0.91 (t, *J* = 7.50 Hz, 3 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ = 155.9 (q), 78.9 (q), 62.6 (s), 50.3 (t), 37.9 (s), 35.4 (s), 32.5 (s), 28.4 (p), 22.0 (s), 19.1 (s), 14.0 (p). IR (film, cm^{-1}) 1168, 1364, 1528, 1682, 2932, 3330. HRMS (ESI$^+$, CH_3OH) m/z: [M + Na]$^+$ Calcd for $C_{13}H_{27}NO_3Na$ 268.1883; Found 268.1883. Spectral data of compound **11e** were in close agreement to those reported in ref.[41]

***tert*-Butyl (10-hydroxydecan-5-yl)carbamate, 11f**. *New product*. Carbamate **11f** was synthesized according to procedure E but with 1.79 g (5.21 mmol) of carbamate **10f**, and 0.26 g (1.03 mmol, 20% in mole) of pyridinium *p*-toluenesulfonate (PPTS). The organic layer was dried over $MgSO_4$ and concentrated to yield an oily residue (1.30 g) which was poured into a chromatographic column (30 × 2.5 cm, diethyl ether) filled with 20 g of silica. The combined fractions were evaporated to afford 1.24 g (92%) of carbamate **11f**. Colorless highly viscous oil. R_f = 0.35 (diethyl ether/petroleum ether, 80:20). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.22 (d, *J* = 8.0 Hz, 1 H, br.), 3.63 (t, *J* = 6.5 Hz, 2 H), 3.60–3.55 (s, 1 H, br.), 1.72–1.68 (s, 1 H, br.), 1.75–1.28 (m, 12 H), 1.45 (s, 9 H), 0.91 (t, *J* = 7.50 Hz, 3 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ = 155.9 (q), 78.9 (q), 62.5 (s), 50.1 (t), 38.0 (s), 35.7 (s), 32.6 (s), 28.4 (p), 25.4 (s), 19.1 (s), 14.0 (p). IR (film, cm^{-1}) 1169, 1364, 1682, 2861, 2931, 3330. HRMS (ESI$^+$, CH_3OH) m/z: [M + Na]$^+$ Calcd for $C_{14}H_{29}NO_3Na$ 282.2034; Found 282.2042.

4-((*tert*-Butoxycarbonyl)amino)heptane-1,7-diyl-dimethanesulfonate, 12a. *New product*. *Procedure F*. An oven dried, 50-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube, and cooled to 0 °C, was successively charged with 20 mL of dichloromethane, 2.13 g (8.61 mmol) of carbamate **11a**, 3.60 mL (2.61 g, 25.82 mmol, 3.0 equiv.) of triethylamine and 0.23 g (1.88 mmol, 0.2 equiv.) of DMAP. The solution was cooled to 0 °C and 2.00 mL (2.95 g, 25.75 mmol, 3.0 equiv.) of methanesulfonyl chloride in 5 mL of dichloromethane was added dropwise over a one-minute period. The reaction mixture was stirred for 5 hours at room temperature and the organic phase was stirred in the presence of *30 mL of saturated $NaHCO_3$ for 4 hours to hydrolyze the excess of methanesulfonyl chloride*. The organic phase was dried over $MgSO_4$ and concentrated to afford a crude reaction mixture (3.50 g) which was dissolved in 3 mL of dichloromethane and poured into a chromatographic column (30 × 2.5 cm, diethyl ether/methanol 98:2) filled with 20 g of silica. The combined fractions were evaporated to afford 2.88 g (83%) of mesylate **12a** as a yellowish highly viscous oil. R_f = 0.40 (diethyl ether/methanol, 98:2). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.34 (d, *J* = 7.0 Hz,

1 H), 4.26 (t, *J* = 6.30 Hz, 4 H), 3.69–3.57 (m, 1 H, br.), 3.02 (s, 6 H), 1.93–1.57 (m, 8 H), 1.44 (s, 9 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 155.8 (q), 79.5 (q), 69.7 (s), 49.3 (t), 37.3 (p), 31.8 (s), 28.4 (p), 25.8 (s). IR (film, cm^{-1}) 949, 1163, 1343, 1520, 1680, 3331. HRMS [ESI^+, CH_2Cl_2/CH_3OH (90:10)] m/z: [M + Na]$^+$ Calcd for $C_{14}H_{29}NO_8NaS_2$ 426.1227; Found 426.1229.

4-((*tert*-Butoxycarbonyl)amino)octane-1,8-diyl-dimethanesulfonate, 12b. *New product.* Mesylate **12b** was synthesized according to procedure F but with 2.61 g (9.98 mmol, 1.0 equiv.) of carbamate **11b**, 4.17 mL (3.03 g, 29.90 mmol, 3.0 equiv.) of triethylamine, 0.27 g (2.21 mmol, 0.2 equiv.) of DMAP and 2.31 mL (3.42 g, 29.90 mmol, 3.0 equiv.) of methanesulfonyl chloride in 20 mL of dichloromethane. The solvent was evaporated in vacuo to yield an oily residue (4.20 g) which was poured into a chromatographic column (30 × 2.5 cm, diethyl ether/methanol, 98:2) filled with 30 g of silica. The combined fractions were evaporated to afford 3.54 g (85%) of mesylate **12b** as a viscous oil. R_f = 0.50 (diethyl ether/methanol, 98:2. ^1H NMR ($CDCl_3$, 300 MHz) δ = 4.28–4.15 (m, 4 H), 4.32 (d, *J* = 7.50 Hz, 1 H, br), 3.66–3.49 (m, 1 H, br.), 3.02 (s, 3 H), 3.01 (s, 3 H), 1.44 (s, 9 H), 1.88–1.36 (m, 10 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 155.8 (q), 79.3 (q), 69.84 (s), 69.76 (s), 49.7 (t), 37.38 (p), 37.34 (p), 35.1 (s), 31.6 (s), 28.8 (s), 28.4 (p), 25.8 (s), 21.9 (s). IR (film, cm^{-1}) 526, 1165, 1342, 1521, 1676, 3356. HRMS [ESI^+, CH_2Cl_2/CH_3OH (90:10)] m/z: [M + Na^+] Calcd for $C_{15}H_{31}NO_8NaS_2$ 440.1383; Found 440.1383. Spectral data of compound **12b** were not reported in ref.[11b]

4-((*tert*-Butoxycarbonyl)amino)nonane-1,9-diyl-dimethanesulfonate, 12c. *New product*. Mesylate **12c** was synthesized according to procedure F but with 1.71 g (6.21 mmol, 1.0 equiv.) of carbamate **11c**, 2.59 mL (1.88 g, 18.58 mmol, 3.0 equiv.) of triethylamine, 0.17 g (1.39 mmol, 0.22 equiv.) of DMAP and 1.44 mL (2.13 g, 18.60 mmol, 3.0 equiv.) of methanesulfonyl chloride in 20 mL of dichloromethane. The solvent was evaporated in vacuo to yield an oily residue (2.70 g) which was poured into a chromatographic column (30 × 2.5 cm, diethyl ether/methanol, 98:2) filled with 30 g of silica. The combined fractions were evaporated to afford 2.19 g (85%) of mesylate **12c** as a colorless solid. R_f = 0.60 (diethyl ether/methanol, 98:2. ^1H NMR ($CDCl_3$, 300 MHz) δ = 4.30–4.18 (m, 5 H), 3.65–3.51 (m, 1 H, br.), 3.02 (s, 3 H), 3.01 (s, 3 H), 1.87–1.56 (m, 6 H), 1.44 (s, 9 H), 1.51–1.32 (m, 6 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 155.8 (q), 79.3 (q), 69.98 (s), 69.94 (s), 49.8 (t), 37.36 (p), 37.30 (p), 35.6 (s), 31.65 (s), 31.56 (s), 29.0 (s), 28.4 (p), 25.8 (s), 25.35 (s), 25.27 (s). IR (film, cm^{-1}) 526, 1165, 1346, 1516, 1692, 2938, 3390. HRMS [ESI^+, CH_2Cl_2/CH_3OH (90:10)] m/z: [M + Na]$^+$ Calcd for $C_{16}H_{33}NO_8NaS_2$ 454.1545; Found 454.1545.

4-((*tert*-Butoxycarbonyl)amino)heptyl-methanesulfonate, 12d. *New product.* Mesylate **12d** was synthesized according to procedure F but with 1.0 g (4.32 mmol) of carbamate **11d**, 0.90 mL (0.65 g, 6.10 mmol, 1.5 equiv.) of triethylamine and 0.13 g (1.08 mmol, 0.25 equiv.) of *N*,*N*-dimethylaminopyridine (DMAP) and 0.50 mL (0.74 g, 6.48 mmol, 1.5 equiv.) of methanesulfonyl chloride. The organic phase was dried over $MgSO_4$ and concentrated to afford a crude reaction mixture (1.3 g) which was dissolved in 3 mL of diethyl ether and poured into a chromatographic column (30 × 2.5 cm, diethyl ether/petroleum ether 20:80) filled with 20 g of silica. The combined fractions were evaporated to afford 1.07 g (80%) of mesylate **12d** as a yellowish highly viscous oil. R_f = 0.50 (diethyl ether ether/petroleum ether, 70:30). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.50 (s, 1 H, br.), 4.25 (t, *J* = 6.50 Hz, 2 H), 3.60–3.50 (s, 1 H, br.), 3.02 (s, 3 H), 1.44 (s, 9 H), 1.54–1.22 (m, 8 H), 0.91 (t, *J* = 7.50 Hz, 3 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ = 155.9 (q), 79.0 (q), 70.1 (s), 49.7 (t), 37.9 (s), 37.2 (p), 31.6 (s), 28.4 (p), 25.7 (s), 19.1 (s), 13.9 (p). HRMS [ESI$^+$, CH_3OH/CH_2Cl_2 (90:10)] m/z: [M + Na]$^+$ Calcd for $C_{13}H_{27}NO_5NaS$ 332.1502; Found 332.1504.

5-((*tert*-Butoxycarbonyl)amino)octyl-methanesulfonate, 12e. Mesylate **12e** was synthesized according to procedure F but with 1.0 g (4.07 mmol) of carbamate **11e**, 0.85 mL (0.62 g, 6.10 mmol, 1.5 equiv.) of triethylamine and 0.124 g (1.01 mmol, 0.25 equiv.) of *N*,*N*-dimethylaminopyridine (DMAP) and 0.47 mL (0.70 g, 6.07 mmol, 1.5 equiv.) of methanesulfonyl chloride. The organic phase was dried over $MgSO_4$ and concentrated to afford a crude reaction mixture (1.3 g) which was dissolved in 3 mL of diethyl ether and poured into a chromatographic column (30 × 2.5 cm, diethyl ether/petroleum ether 20:80) filled with 20 g of silica. The combined fractions were evaporated to afford 1.07 g (82%) of mesylate **12e** as a yellowish highly viscous oil. R_f = 0.50 (diethyl ether ether/petroleum ether, 70:30). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.30 (d, *J* = 8.0 Hz, 1 H, br.), 4.21 (t, *J* = 6.50 Hz, 2 H), 3.60–3.50 (s, 1 H, br.), 3.00 (s, 3 H), 1.66–1.54 (m, 2 H), 1.42 (s, 9 H), 1.54–1.22 (m, 8 H), 0.88 (t, *J* = 7.50 Hz, 3 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ = 155.8 (q), 78.9 (q), 70.0 (s), 50.0 (t), 37.8 (s), 37.3 (p), 35.0 (s), 28.9 (s), 28.4 (p), 21.8 (s), 19.1 (s), 14.0 (p). IR (film, cm^{-1}) 527, 1165, 1346, 1516, 1690, 2938, 3390. HRMS [ESI$^+$, CH_3OH/CH_2Cl_2 (90:10)] m/z: [M + Na$^+$] Calcd for $C_{14}H_{29}NO_5NaS$ 346.1664; Found 346.1658. Spectral data of compound **12e** agreed with those reported in ref.[11b]

6-((*tert*-Butoxycarbonyl)amino)nonyl-methanesulfonate, 12f. *New product*. Mesylate **12f** was synthesized according to procedure F but with 1.66 g (6.40 mmol) of carbamate **11f**, 1.34 mL (0.97 g, 6.10 mmol, 1.5 equiv.) of triethylamine and 0.17 g (1.40 mmol, 0.22 equiv.) of *N*,*N*-dimethylaminopyridine (DMAP) and 0.74 mL (1.09 g, 9.56 mmol, 1.5 equiv.) of methanesulfonyl chloride. The organic phase was dried over $MgSO_4$ and concentrated to afford a crude reaction

mixture (1.3 g) which was dissolved in 3 mL of diethyl ether and poured into a chromatographic column (30 × 2.5 cm, diethyl ether/petroleum ether 20:80) filled with 20 g of silica. The combined fractions were evaporated to afford 2.13 g (93%) of mesylate **12f** as a yellowish highly viscous oil. R_f = 0.60 (diethyl ether ether/petroleum ether, 70:30). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.30 (s, 1 H, br.), 4.22 (t, *J* = 6.50 Hz, 2 H), 3.60–3.50 (s, 1 H, br.), 3.00 (s, 3 H), 1.75 (quint. *J* = 7.5 Hz, 2 H), 1.42 (s, 9 H), 1.50–1.28 (m, 10 H), 0.91 (t, *J* = 7.50 Hz, 3 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ = 155.8 (q), 78.9 (q), 70.0 (s), 50.2 (t), 37.9 (s), 37.4 (p), 35.0 (s), 29.1 (s), 28.4 (p), 25.39 (s), 25.35 (s), 19.1 (s), 14.0 (p). IR (film, cm^{-1}) 527, 1168, 1351, 1516, 1690, 2934, 3392. HRMS (ESI$^+$, CH_3OH) m/z: [M + Na]$^+$ Calcd for $C_{15}H_{31}NO_5NaS$ 360.1815; Found 360.1815.

4-Aminoheptane-1,7-diyl-dimethanesulfonate hydrochloride salt, 13a. *New product*. <u>*Procedure G*</u>. An oven dried, 50-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube, was successively charged with a solution of mesylate **12a** (1.00 g, 2.48 mmol) in dioxane (10 mL) and 10 mL of a 4 M solution of HCl in dioxane. The resulting solution was stirred for 24 h and the solvent was evaporated to dryness in vacuo. The resulting paste was taken-up with diethyl ether (10 mL x 3) until the obtaining of a white solid which was dried under reduced pressure on a fritted glassware to afford 0.68 g (81%) of hydrochloride salt **13a** as a white solid. M.p. = 170-172 °C.[31] ^{1}H NMR (D_2O, 300 MHz) δ = 4.32 (t, *J* = 5.70 Hz, 4 H), 3.23 (quint., *J* = 7.50 Hz, 1 H), 3.12 (s, 3 H), 1.90–1.60 (m, 10 H). ^{13}C{^{1}H} NMR (D_2O, 75 MHz) δ = 71.0 (s), 50.7 (t), 36.3 (s), 27.8 (s), 24.2 (s). IR (neat, cm^{-1}) 525, 973, 1341, 1605, 2926. HRMS (ESI$^+$, H_2O) m/z: C$^+$ Calcd for $C_9H_{22}NO_6S_2$ 304.0883; Found 304.0887.

4-Aminooctane-1,8-diyl-dimethanesulfonate hydrochloride salt, 13b. *New product*. Hydrochloride salt **13b** was synthesized according to procedure G but with 1.56 g (3.73 mmol) of mesylate **12b** to afford 0.68 g (81%) of hydrochloride salt **13b** as a white hygroscopic solid. M.p. = 158-160 °C.[31] ^{1}H NMR (D_2O, 300 MHz) δ = 4.28–4.23 (m, 4 H), 3.23 (q, *J* = 7.50 Hz, 1 H), 3.15 (s, 3 H), 3.14 (s, 3 H), 1.80–1.40 (m, 10 H). ^{13}C{^{1}H} NMR (D_2O, 75 MHz) δ = 71.6 (s), 71.1 (s), 51.1 (t), 36.3 (s), 30.9 (s), 28.0 (s), 27.8 (s), 24.3 (s), 20.4 (s). IR (neat, cm^{-1}) 525, 922, 1164, 2932. HRMS [ESI$^+$, CH_2Cl_2/CH_3OH (90:10)] m/z: C$^+$ Calcd for $C_{10}H_{24}NO_6S_2$ 318.1039; Found 318.1039.

4-Aminononane-1,9-diyl-dimethanesulfonate hydrochloride salt, 13c. *New product*. Hydrochloride salt **13c** was synthesized according to procedure G but with 1.35 g (3.13 mmol) of mesylate **12c** to afford 0.85 g (74%) of hydrochloride salt **13c** as a white hygroscopic solid. M.p. = 153-155 °C.[31] ^{1}H NMR (D_2O, 300 MHz) δ = 4.38–4.32 (m, 4 H), 3.23 (q, *J* = 7.50 Hz, 1 H), 3.20 (s, 3 H), 3.19 (s, 3 H),

1.90–1.60 (m, 8 H), 1.50–1.40 (m, 4 H). $^{13}C\{^1H\}$ NMR (D_2O, 75 MHz) δ = 72.1 (s), 71.1 (s), 51.1 (t), 36.31 (p), 36.27 (p), 31.4 (s), 28.0 (s), 27.9 (s), 24.4 (s), 24.3 (s), 23.6 (s). IR (neat, cm^{-1}) 525, 922, 1164, 2932. HRMS [ESI^+, CH_2Cl_2/CH_3OH (90:10)] m/z: C^+ Calcd for $C_{11}H_{26}NO_6S_2$ 332.1196; Found 332.1197.

Hexahydro-1*H*-pyrrolizine hydrochloride salt, 1•HCl. *New product*. *Procedure H*. To a solution of 0.60 g (1.76 mmol) of hydrochloride salt **13a** dissolved in 1 mL of water and cooled to 0 °C, was added 0.21 g (5.25 mmol, 3.0 equiv.) of powdered sodium hydroxide. The solution was stirred for 30 minutes to yield hexahydro-1*H*-pyrrolizine **1** a colourless highly volatile oil in suspension in water. This oil was extracted with 2 mL of diethyl ether (x 3) and the combined ethereal layers were dried over $MgSO_4$. Then, 1 mL of a 2 M solution of HCl in diethyl ether was added causing the precipitation of pyrrolizidine hydrochloride salt **1**•HCl which was taken-up (x 3) in 5 mL of diethyl ether and filtrated over a fritted glassware. The resulting solid was triturated 3 times with anhydrous diethyl ether to afford 0.20 g (75%) of hydrochloride salt **1**•HCl as a colourless solid. M.p. = 212 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ = 12.5 (s, 1 H, br.), 4.11 (quint., *J* = 6.50 Hz, 1 H), 3.68–3.76 (m, 2 H), 2.83–2.91 (m, 2 H), 2.21–2.33 (m, 2 H), 2.06–2.16 (m, 4 H), 1.80–1.69 (m, 2 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 67.0 (t), 54.6 (s), 31.1 (s), 25.4 (s).^1H NMR (D_2O, 300 MHz) δ = 4.11 (quint., *J* = 6.50 Hz, 1 H), 3.42–3.50 (m, 2 H), 2.96–3.04 (m, 2 H), 1.95–2.16 (m, 4 H), 1.75–1.90 (m, 2 H), 1.67–1.75 (m, 2 H). $^{13}C\{^1H\}$ NMR (D_2O, 75 MHz) δ = 68.4 (s), 55.0 (s), 30.3 (s), 24.5 (s). IR (neat, cm^{-1}) 525, 973, 1172, 2927. HRMS (ESI^+, H_2O) m/z: C^+ Calcd for $C_7H_{14}N$ 112.1121; Found 112.1120. To the best of our knowledge, spectral data of pyrrolizidine hydrochloride have not been reported so far.

Octahydroindolizine hydrochloride salt, δ-coniceine hydrochloride salt, 2•HCl. **Synthesis of δ-coniceine 2.** To a solution of 0.45 g (1.27 mmol) of hydrochloride salt **13b** dissolved in 1 mL of water and cooled to 0 °C, was added 0.15 g (3.90 mmol, 3.0 equiv.) of powdered sodium hydroxide. The solution was stirred for 30 minutes upon which a pale oil gradually decanted. After a 12 h standing in an NMR tube, δ-coniceine **2** (0.12 g, 76%) was obtained as a colourless highly volatile oil. ^1H NMR ($CDCl_3$, 300 MHz) δ = 3.12–3.01 (m, 2 H), 2.11–1.92 (m, 3 H), 1.88–1.58 (m, 5 H), 1.45–1.34 (m, 1 H), 1.28–1.12 (m, 2 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 64.5 (t), 54.2 (s), 53.1 (s), 31.0 (s), 30.5 (s), 25.4 (s), 24.5 (s), 20.6 (s). Spectral data of compound **2** were in close agreement to those reported in ref.[11b] Hydrochloride salt **2**•HCl was synthesized according to procedure H but with 0.50 g (1.41 mmol) of hydrochloride salt **13b** to afford 0.19 g (83%) of hydrochloride salt **2**•HCl as a colorless solid. M.p. = 162 °C. ^1H NMR (CD_3OD, 300 MHz, mixture of two diastereoisomers (90:10), major diastereoisomer) δ = 3.68–3.57 (m, 2 H), 3.20–2.91 (m, 3 H), 2.35–2.25 (m, 1 H), 2.19–1.95 (m, 5 H),

1.87–1.50 (m, 5 H). $^{13}C\{^1H\}$ NMR (CD_3OD, 75 MHz, mixture of two diastereoisomers (90:10), major diastereoisomer) δ = 67.9 (t), 53.6 (s), 52.7 (s), 29.4 (s), 29.1 (s), 24.3 (s), 23.4 (s), 20.3 (s). IR (neat, cm^{-1}) 525, 973, 1172, 2927. HRMS (ESI^+, CH_3OH) m/z: C^+ Calcd for $C_8H_{16}N$ 126.1277; Found 126.1277. These spectral data were in close agreement to those reported in ref.[41]

***tert*-Butyl 2-propylpyrrolidine-1-carboxylate, 14a**. *Procedure I.* An oven dried, 10-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube, and cooled to 0 °C, was successively charged with 3 mL of anhydrous DMF and 0.30 g of NaH (60% in dispersion in mineral oil, 0.18 g, 7.50 mmol, 5.80 equiv.). Then, 0.40 g (1.29 mmol, 1.0 equiv.) of mesylate **12d** were slowly added to the previous suspension which was stirred for 2 hours at room temperature. The reaction was quenched by the slow addition of 20 mL of water to yield an oily residue which was extracted (x 3) with 20 mL of diethyl ether. The combined organic phases were dried over $MgSO_4$ and concentrated to afford a crude reaction mixture (0.30 g) which was poured into a chromatographic column (30 × 2.5 cm, petroleum ether/diethyl ether 90:10) filled with 12 g of silica. The combined fractions were evaporated to afford 0.206 g (75%) of *N*-Boc-pyrrolidine **14a**. Colorless viscous oil, R_f = 0.20 (petroleum ether/diethyl ether, 95:5). ^1H NMR [$CDCl_3$, 300 MHz, 2 rotamers, splitting signals are indicated with an asterisk (*)] δ = 3.89–3.66 (s, 1 H, br), 3.45–3.20 (m, 2 H), 1.95–1.56 (m, 5 H), 1.46 (s, 9 H), 1.37–1.21 (m, 3 H), 0.92 (t, *J* = 7.10 Hz, 3 H). $^{13}C\{^1H\}$ NMR [$CDCl_3$, 75 MHz, 2 rotamers, splitting signals are indicated with an asterisk (*)] δ = 154.8 (q), 78.8 (q), 57.0 (t), [46.4 (s), 46.0 (s)]*, [36.9 (s), 36.4 (s)]*, [30.6 (s), 29.7 (s)]*, 28.6 (p), [23.8 (s), 23.1 (s)]*, 19.6 (s), 14.1 (p). IR (film, cm^{-1}) 1143, 1414, 1687, 2930. HRMS (ESI^+, CH_3OH) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{23}NO_2Na$ 236.1621; Found 236.1623. Spectral data of compound **14a** were in close agreement to those reported in ref.[42]

***tert*-Butyl 2-propylpiperidine-1-carboxylate, 14b**. *N*-Boc-coniine **14b** was synthesized according to procedure I but with 0.33 g (1.02 mmol, 1.0 equiv.) of mesylate **14e** and 0.23 g of NaH (60% in dispersion in mineral oil, 0.14 g, 5.91 mmol, 5.80 equiv.). The solvent was evaporated in vacuo to yield an oily residue (0.30 g) which was poured into a chromatographic column (30 × 2.5 cm, petroleum ether/diethyl ether, 60:40) filled with 5.0 g of silica. The combined fractions were evaporated to afford 0.19 g (82%) of *N*-Boc-coniine as a colorless highly viscous oil. Colorless viscous oil, R_f = 0.30 (petroleum ether/diethyl ether, 95:5). ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.20 (s, 1 H, br.), 3.95 (dm, *J* = 13.5 Hz, 1 H), 2.74 (t, *J* = 13.5 Hz, 1 H), 1.45 (s, 9 H), 1.70–1.21 (m, 10 H), 0.92 (t, *J* = 7.30 Hz, 3 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ = 155.1 (q), 78.9 (q), 50.1 (s, br.), 38.6 (t, br.), 31.9 (s), 28.5 (p), 25.7 (s), 19.4 (s), 19.0 (s), 14.0 (p). IR (film, cm^{-1}) 1143, 1414, 1686, 2930. HRMS [ESI^+,

CH_3OH/CH_2Cl_2 (90:10)] m/z: [M + Na]$^+$ Calcd for $C_{13}H_{25}NO_2Na$ 250.1778; Found 250.1778. Spectral data of compound **14b** were in close agreement to those reported in ref.[43]

***tert*-Butyl 2-propylazepane-1-carboxylate, 14c**. *New product*. Procedure J. An oven dried, 10-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube, was successively charged with 2 mL of anhydrous DMF and 0.55 g of NaH (60% in dispersion in mineral oil, 0.33 g, 13.75 mmol, 10.0 equiv.). The suspension was heated in a sand bath to 75 °C and 0.45 g (1.33 mmol, 1.0 equiv.) of mesylate **12f** (dissolved in 2 mL of DMF) were slowly added at that temperature. Stirring was continued for 2 hours at 75 °C and the reaction mixture was cooled to 0 °C. The reaction was quenched by the slow addition of 20 mL of water to yield an oily residue which was extracted (x 3) with 20 mL of diethyl ether. The combined organic phases were dried over $MgSO_4$ and concentrated to afford a crude reaction mixture (0.30 g) which was poured into a chromatographic column (30 × 2.5 cm, petroleum ether/diethyl ether 90:10) filled with 12 g of silica. The combined fractions were evaporated to afford 0.225 g (70%) of carbamate **14c** as a colorless viscous oil. Colorless viscous oil, R_f = 0.85 (diethyl ether/petroleum ether, 70:30). ^{1}H NMR [$CDCl_3$, 300 MHz, 2 rotamers, splitting signals are indicated with an asterisk (*)] δ = [4.13–4.00 (m, 0.5 H), 3.95–3.84 (m, 0.5 H)]*, [3.72 (dm, *J* = 11.9 Hz, 0.5 H), 3.59 (dm, *J* = 11.9 Hz, 0.5 H),]*, 2.65 (ddd, *J* = 14.4, 11.2, 1.8 Hz, 1 H), 2.08–1.94 (m, 1 H), 1.45 (s, 9 H), 1.85–1.07 (m, 11 H), 0.89 (t, *J* = 7.10 Hz, 3 H). ^{13}C{^{1}H} NMR [$CDCl_3$, 75 MHz, 2 rotamers, splitting signals are indicated with an asterisk (*)] δ = [156.0 (q), 155.8 (q)]*, [78.9 (q), 78.6 (q)]*, [54.9 (s), 54.1 (s)]*, [41.6 (s), 41.3 (s)]*, [37.5 (s), 37.4 (s)]*, [34.8 (s), 34.4 (s)]*, 30.0 (s), 28.6 (p), [29.0 (s), 28.5 (s)]*, [25.2 (s), 24.9 (s)]*, [19.5 (s), 19.4 (s)]*, [14.24 (p),14.16 (p)]*. IR (film, cm^{-1}) 1162, 1411, 1686, 2929. HRMS (ESI$^+$, CH_3OH/CH_2Cl_2 (90:10)] m/z: [M + Na]$^+$ Calcd for $C_{14}H_{27}NO_2Na$ 264.1934; Found 264.1937.

2-propylazepane, hydrochloride salt, 15a•HCl. An oven dried round bottom flask fitted with a magnetic stirred was successively charged with 0.10 g (0.414 mmol) of carbamate **14c** and 2 mL of a 2 M solution of HCl in dioxane. The resulting solution was stirred for 24 h and the solvent was evaporated to dryness in vacuo. The resulting paste was taken-up with diethyl ether (10 mL x 3) until the obtaining of a white solid which was dried under reduced pressure on a fritted glassware to afford 0.057 g (77%) of hydrochloride salt **15a•HCl.** White solid, M.p. = 175 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 9.50 (s, 1 H, br.), 9.21 (s, 1 H, br.), 3.36–3.09 (m, 3 H), 2.10–1.39 (m, 12 H), 0.95 (t, *J* = 7.25 Hz, 3 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ = 58.8 (t), 45.1 (s), 35.9 (s), 30.5 (s), 27.0 (s), 25.0 (s), 24.8 (s), 19.2 (p), 13.8 (p). IR (neat, cm^{-1}) 1074, 1448, 1588, 2763. HRMS (ESI$^+$, CH_3OH) m/z: C$^+$ Calcd for

$C_9H_{20}N$ 142.1590; Found 142.1590. Spectral data of compound **15a•**HCl were in close agreement to those reported in ref.[34]

(((5-Iodopentyl)oxy)methyl)benzene, 5i. *Synthesis of 5-(benzyloxy)pentan-1-ol*. An oven dried, 250-mL, three-necked round bottom flask, fitted with a magnetic stirring bar, connected to an argon inlet tube and cooled to 0 °C, was successively charged with 30 mL of anhydrous THF, 20.12 mL (20.0 g, 192.0 mmol, 5 equiv.) of pentane-1,5-diol. Then, 1.83 g of NaH (60% in dispersion in mineral oil, 1.10 g, 45.83 mol, 1.20 equiv.) were slowly added to the previous solution, and stirring was continued until evolution of hydrogen had ceased. After 1 hour, 4.56 mL (6.57 g, 38.41 mol, 1.0 equiv.) of benzylbromide were slowly added by syringe and the resulting suspension (NaBr) was stirred for 12 hours at ambient temperature and refluxed for 4 hours. The solvent was evaporated under reduced pressure to yield an oily residue which was taken-up in a mixture of water (100 mL) and diethyl ether (200 mL). The aqueous layer was discarded and the ethereal layer was washed (x3) with 100 mL of water to remove the 1,4-butanediol in excess. The organic layer was dried over $MgSO_4$ and concentrated to afford a crude reaction mixture which was and poured into a chromatographic column (30 × 5 cm, petroleum ether/diethyl ether 80:20) filled with 150 g of silica. The combined fractions were evaporated to afford 5.96 g (81%) of 5-(benzyloxy)pentan-1-ol as a colorless oil. R_f = 0.35 (diethyl ether/petroleum ether, 80:20). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.35–7.22 (m, 5 H), 4.48 (s, 2 H), 3.57 (t, *J* = 6.4 Hz, 2 H, br.), 3.46 (t, *J* = 6.5 Hz, 2 H), 2.20 (s, large, 1 H), 1.67–1.50 (m, 4 H), 1.47–1.37 (m, 2 H). *Synthesis of iodide **5i***. A 200-mL, one necked Schlenk tube, fitted with a magnetic stirring bar, and connected to an argon inlet tube was successively charged with 100 mL of dichloromethane, 5.95 g (30.62 mmol, 1.0 equiv.) of 5-benzyloxy)pentan-1-ol, 4.17 g (61.25 mmol, 2.0 equiv.) of imidazole, 10.4 g (39.65 mmol, 1.30 equiv.) of triphenylphosphine. The resulting solution was cooled to 0 °C, then, 10.88 g (42.86 mmol, 1.40 equiv.) of molecular iodine were added portion wise over a 20 minutes period. The resulting orange solution was warmed up to ambient temperature and stirring was continued for 2 hours before the addition of 100 mL of water containing 5.0 g of sodium sulfite. The biphasic system was vigorously stirred for 30 minutes and the organic phase was washed with 50 mL of water (x 3), dried over $MgSO_4$, and concentrated to yield a colorless solid which was taken-up in a mixture (50 mL) of petroleum ether and diethyl ether (75:25) until the precipitation of triphenylphosphine oxide which was removed by filtration over a sintered glass filter. The filtrate was concentrated to yield 10.1 g a colorless paste which was dissolved in 5 ml of diethyl ether and poured into a chromatographic column (30 × 2.5 cm, petroleum ether/diethyl ether 80:20) filled with 100 g of silica. The combined fractions were evaporated *in vacuo* at a temperature of 40 °C to afford 7.98 g (86%) of iodide **5i** as a yellowish oil. R_f = 0.70 (petroleum ether/diethyl ether, 90:10). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.36–7.24 (m, 5 H), 4.49 (s, 2 H), 3.47 (t, *J* =

6.2 Hz, 2 H), 3.18 (t, *J* = 7.0 Hz, 2 H), 1.83 (quint., *J* = 7.3 Hz, 2 H), 1.68–1.58 (m, 2 H), 1.54–1.43 (m, 2 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 138.5 (q), 128.3 (t), 127.6 (t), 127.5 (t), 72.9 (s), 70.0 (s), 33.3 (s), 28.7 (s), 27.2 (s), 6.9 (s). IR (film, cm^{-1}): 696, 1027, 1171, 1452, 2855, 2933, 3028. HRMS [ESI^+, CH_3OH/CH_2Cl_2 (95:5)] m/z: $[M + Na]^+$ Calcd for $C_{12}H_{17}IONa$ 327.0216; Found 327.0217. Spectral data of compound **5i** were in close agreement to those reported in ref.[36]

7-(benzyloxy)-2-(dibenzylamino)heptanenitrile, 6i. *New product*. The synthesis of α-aminonitrile **6i** was carried out according to procedure A, but with 2.50 g (10.55 mmol) of α-aminonitrile **4** and 2.80 g (9.20 mmol, 1.10 equiv.) of iodide **5i** as the alkylating agent. The crude oily residue (4.50 g) was diluted in 10 mL of a mixture of diethyl ether and petroleum ether (70:30) and poured into a chromatographic (30 × 4.7 cm, petroleum ether/diethyl ether, 95:5) filled with 70 g of silica. The combined fractions were evaporated to afford 3.52 g (81%) of α-aminonitrile **6i** as a highly viscous oil. R_f = 0.30 (petroleum ether/diethyl ether, 97:3). ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.39–7.22 (m, 15 H), 4.46 (s, 2 H), 3.94 (d, *J* = 13.5 Hz, 2 H), 3.51 (t, *J* = 7.8 Hz, 1 H), 3.39 (t, *J* = 6.4 Hz, 2 H), 3.37 (d, *J* = 13.5 Hz, 2 H), 1.91–1.70 (m, 2 H), 1.55 (quint., *J* = 7.0 Hz, 2 H), 1.48–1.18 (m, 4 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ = 138.5 (q), 137.6 (q), 128.8 (t), 128.6 (t), 128.4 (t), 127.6 (t), 127.5 (t), 117.5 (q), 72.9 (s), 70.0 (s), 55.4 (s), 52.7 (t), 31.2 (s), 29.4 (s), 25.6 (s), 25.4 (s). IR (neat, cm^{-1}): 696, 1098, 1365, 2221, 2857, 3029. HRMS [ESI^+, CH_3OH/CH_2Cl_2 (95:5)] m/z: $[M + Na]^+$ Calcd for $C_{28}H_{32}N_2ONa$ 435.2407; Found 435.2406.

***N*,*N*-Dibenzyl-9-(benzyloxy)-1-((tetrahydro-2*H*-pyran-2-yl)oxy)nonan-4-amine, 8g**. *New product*. The synthesis of amine **8g** was carried out according to procedure B, but with 4.30 g (10.42 mmol, 1.00 equiv.) of α-aminonitrile **6i** and 3.65 g (13.55 mmol, 1.30 equiv.) of 2-(3-iodopropoxy)tetrahydro-2*H*-pyran (**5a**) as the alkylating agent. The crude oily residue (6.10 g) was diluted in 10 mL of a mixture or petroleum ether and diethyl ether (80:20) and poured into a chromatographic (30 × 5.0 cm, petroleum ether/diethyl ether, 70:30) filled with 70 g of silica. The combined fractions were evaporated to afford 3.86 g (80%) of amine **8g** as a colorless highly viscous oil. R_f = 0.20 (petroleum ether/diethyl ether, 90:10). ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.41–7.14 (m, 15 H), 4.50 (s, 2 H), 4.45–4.53 (m, 1 H), 3.90–3.78 (m, 1 H), 3.58 (d, *J* = 12.5 Hz, 2 H), 3.50 (d, *J* = 12.5 Hz, 2 H), 3.42 (t, *J* = 6.50 Hz, 2 H), 3.70–3.37 (m, 2 H), 3.32–3.21 (m, 1 H), 2.43 (quint., *J* = 6.50 Hz, 1 H), 1.85–1.46 (m, 12 H), 1.40–1.12 (m, 6 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, 2 diastereoisomers) δ = 140.7 (q), 138.7 (q), 129.9 (t), 128.3 (t), 128.0 (t), 127.6 (t), 127.4 (t), 126.6 (t), 98.9 (t), 98.8 (t), 72.9 (s), 70.4 (s), 67.8 (s), 67.6 (s), 62.4 (s), 56.9 (s), 56.8 (s), 53.3 (t), 30.8 (s), 27.3 (s), 27.2 (s), 27.05 (s), 27.01 (s), 26.4 (s), 26.3 (s),

25.5 (s), 19.7 (s). IR (film, cm^{-1}) 696, 1027, 1075, 2854, 2934, 3061. HRMS [ESI^+, CH_2Cl_2/CH_3OH (90:10)] m/z: $[M + H]^+$ Calcd for $C_{35}H_{48}NO_3$ 530.3629; Found 530.3629.

6-Amino-9-((tetrahydro-2*H*-pyran-2-yl)oxy)nonan-1-ol, 9g. *New product*. The synthesis of amine **9g** has been carried out according to procedure C, but with 30 mL of ethanol and 10 mL of methanol, 0.30 g (8% in mass) of 20% $Pd(OH)_2/C$ and 3.70 g (6.98 mmol) of amine **8g**. The suspension was stirred for 72 h at 60 °C and the filtrate was concentrated under reduced pressure, to afford amine **9g** (1.78 g, 98%) which was utilized in the next step without purification. R_f = 0.20 (dichloromethane/methanol, 90:10). ^1H NMR ($CDCl_3$, 300 MHz, 2 diastereoisomers) δ = 4.59–4.56 (m, 1 H), 3.90–3.82 (m, 1 H), 3.79–3.70 (m, 1 H), 3.55–3.46 (m, 1 H), 3.43–3.36 (m, 1 H), 2.79–2.67 (m, 1 H), 3.61 (t, *J* = 6.5 Hz, 2 H), 1.90–1.22 (m, 21 H). $^{13}C\{^1H\}$ NMR [$CDCl_3$, 75 MHz, 2 diastereoisomers, splitting signals are indicated with an asterisk (*)] δ = [98.90 (t), 98.88 (t)]*, [67.68 (s), 67.65 (s)]*, 62.4 (s), [51.00 (t), 50.96 (t)]*, 37.4 (s), 34.8 (t), 32.7 (s), 30.7 (s), [26.43 (s), 26.37 (s)]*, [25.93 (s), 25.89 (s)]*, 25.5 (s), 19.7 (s). IR (film, cm^{-1}) 1027, 1118, 1352, 2854, 2926, 3355. HRMS [ESI^+, CH_3OH/CH_2Cl_2 (90:10)] m/z $[M + H]^+$ Calcd for $C_{14}H_{30}NO_3$ 260.2220; Found 260.2219.

***tert*-Butyl (9-hydroxy-1-((tetrahydro-2*H*-pyran-2-yl)oxy)nonan-4-yl)carbamate, 10g**. *New product*. Carbamate **10g** was synthesized according to procedure D but with 0.34 g (1.31 mmol) of amine **9g** and 0.286 g (1.31 mmol, 1.0 equiv.) of Boc_2O. The solvents were evaporated in vacuo to yield an oily residue (0.41 g) which was poured into a chromatographic column (30 × 2.5 cm, diethyl ether) filled with 30 g of silica. The combined fractions were evaporated to afford 0.40 g (85%) of carbamate **10g** as a yellowish highly viscous oil. R_f = 0.5 (diethyl ether). ^1H NMR ($CDCl_3$, 300 MHz, 2 diastereoisomers) δ = 4.59–4.54 (m, 1 H), 4.43–4.32 (m, 1 H), 3.88–3.83 (m, 1 H), 3.78–3.70 (m, 1 H), 3.67–3.57(m, 3 H), 3.54–3.46 (m, 1 H), 3.43–3.34 (m, 1 H), 1.44 (s, 9 H), 1.86–1.30 (m, 19 H). $^{13}C\{^1H\}$ NMR [$CDCl_3$, 75 MHz, 2 diastereoisomers, splitting signals are indicated with an asterisk (*)] δ = 155.9 (q), [99.0 (t), 98.9 (t)]*, 78.9 (q), 67.4 (s), [62.5 (s), 62.4 (s)]*, 50.2 (t), 35.7 (s), 32.6 (s), [30.76 (s), 30.74 (s)]*, 28.4 (p), [26.2 (s), 26.1 (s)]*, [25.47 (s), 25.37 (s)]*, [19.76 (s), 19.72 (s)]*. IR (film, cm^{-1}) 867, 1168, 1524, 1686, 2859, 2933, 3337. HRMS (ESI^+, CH_3OH) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{37}NO_5Na$ 382.2564; Found 382.2567.

6-((*tert*-Butoxycarbonyl)amino)-9-((tetrahydro-2*H*-pyran-2-yl)oxy)nonyl methanesulfonate, 12g. *New product*. Mesylate **12g** was synthesized according to procedure F but with 1.91 g (5.31 mmol, 1.0 equiv.) of carbamate **10g**, 1.10 mL (0.80 g, 7.90 mmol, 1.50 equiv.) of triethylamine, 0.14 g (1.14 mmol, 0.22 equiv.) of DMAP and 0.61 mL (0.91 g, 7.94 mmol, 1.5 equiv.) of methanesulfonyl chloride

in 20 mL of dichloromethane. The solvent was evaporated in vacuo to yield an oily residue (2.50 g) which was poured into a chromatographic column (30 × 2.5 cm, diethyl ether/methanol, 98:2) filled with 30 g of silica. The combined fractions were evaporated to afford 2.05 g (88%) of mesylate **12g** as a colorless oil. R_f = 0.60 (diethyl ether/petroleum ether, 80:20. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.58–4.53 (m, 1 H), 4.38–4.34 (m, 1 H), 4.22 (t, *J* = 6.5 Hz, 2 H), 3.89–3.82 (m, 1 H), 3.78–3.70 (m, 1 H), 3.62–3.45 (m, 2 H), 3.44–3.34 (m, 1 H), 3.00 (s, 3 H), 1.44 (s, 9 H), 1.86–1.30 (m, 18 H). ^{13}C{^{1}H} NMR [$CDCl_3$, 75 MHz, 2 diastereoisomers, splitting signals are indicated with an asterisk (*)] δ = 155.8 (q), [99.0 (t), 98.9 (t)]*, 78.9 (q), 70.0 (s), 67.4 (s), [62.54 (s), 62.47 (s)]*, 50.3 (t), 37.4 (p), 35.5 (s), 32.1 (s), [30.76 (s), 30.73 (s)]*, 29.1 (s), 28.4 (p), [26.17 (s), 26.12 (s)]*, [25.45 (s), 25.37 (s)]*, 19.74 (s). IR (film, cm^{-1}) 527, 1021, 1169, 1351, 1517, 1694, 2863, 2938, 3341. HRMS [ESI$^+$, CH_2Cl_2/CH_3OH (90:10)] [M + Na]$^+$ Calcd for $C_{20}H_{39}NO_7NaS$ 460.2340; Found 460.2344.

***tert*-Butyl 2-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)propyl)azepane-1-carboxylate, 14d**. *New product*. Azepane **14d** was synthesized according to procedure J but with 1.32 g (3.03 mmol, 1.0 equiv.) of mesylate **12g** and 1.22 g of NaH (60% in dispersion in mineral oil, 0.727 g, 30.3 mmol, 10.0 equiv.). The solvent was evaporated in vacuo to yield an oily residue (0.90 g) which was poured into a chromatographic column (30 × 2.5 cm, petroleum ether/diethyl ether, 60:40) filled with 5.0 g of silica. The combined fractions were evaporated to afford 0.72 g (70%) of azepane **14d** as a colorless highly viscous oil. R_f = 0.3 (petroleum ether/diethyl ether, 70:30). ^{1}H NMR ($CDCl_3$, 300 MHz, 2 rotamers and diastereoisomers) δ = 4.58–4.52 (m, 1 H), 4.13–4.04 (m, 1 H), 3.92–3.82 (m, 1 H), 3.77–3.68 (m, 1 H), 3.59 (dm, *J* = 12.0 Hz, 1 H), 3.53–3.44 (m, 1 H), 3.42–3.32 (m, 1 H), 2.66 (tm, *J* = 12.0 Hz, 1 H), 2.11–1.97 (m, 1 H), 1.45 (s, 9 H), 1.89–1.39 (m, 13 H), 1.29–1.11 (m, 4 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, 2 rotamers and diastereoisomers) δ = 156.0 (q), 155.8 (q), 98.9 (t), 79.0 (q), 78.7 (q), 67.7 (s), 67.4 (s), 62.4 (s), 55.3 (t), 55.1 (t), 54.1 (t), 41.7 (s), 41.3 (s), 34.8 (s), 34.4 (s), 31.9 (s), 31.8 (s), 31.6 (s), 30.8 (s), 29.0 (s), 28.6 (p), 28.4 (s), 26.7 (s), 26.5 (s), 25.5 (s), 25.2 (s), 24.9 (s), 19.76 (s), 19.72 (s). IR (film, cm^{-1}) 1158, 1363, 1410, 1685, 2853, 2925. HRMS [ESI$^+$, CH_3OH/CH_2Cl_2 (90:10)] m/z: [M + Na]$^+$) Calcd for $C_{19}H_{35}NO_4Na$ 364.2458; Found 364.2461.

***tert*-Butyl 2-(3-hydroxypropyl)azepane-1-carboxylate, 14e**. *New product*. Carbamate **14e** was synthesized according to procedure E but with 1.30 g (3.80 mmol) of carbamate **14d**, and 0.19 g (0.75 mmol, 20% in mole) of pyridinium *p*-toluenesulfonate (PPTS). The solvent was removed under reduced pressure, and the crude material was stirred for 15 minutes in a biphasic mixture of diethyl ether (100 mL) and water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated to yield an oily residue (1.10 g) which was poured into a chromatographic column (30 × 2.5 cm, diethyl ether)

filled with 20 g of silica. The combined fractions were evaporated to afford 0.92 g (94%) of carbamate **14e**. Colorless highly viscous oil. R_f = 0.6 (diethyl ether/petroleum ether, 70:30). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.19–4.04 (m, 0.55 H, br.), 3.96–3.84 (m, 0.45 H, br.), 3.80–3.54 (m, 3 H), 2.66 (ddd, *J* = 13.6, 11.3, 1.8 Hz, 1 H), 2.14–2.00 (m, 1 H), 1.94 (s, 1 H, br.), 1.46 (s, 9 H), 1.84–1.40 (m, 7 H), 1.28–1.00 (m, 4 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, 2 rotamers (95:5), major rotamer) δ = 156.5 (q), 79.1 (q), 63.0 (s), 54.1 (t), 41.6 (s), 34.7 (s), 31.8 (s), 30.0 (s), 29.0 (s), 28.9 (s), 28.6 (p), 25.0 (s). IR (film, cm^{-1}) 1155, 1412, 1663, 2854, 2926, 3430. HRMS [ESI$^+$, CH_3OH/CH_2Cl_2 (90:10)] m/z: [M + Na]$^+$ Calcd for $C_{14}H_{27}NO_3Na$ 280.1883; Found 280.1884.

***tert*-Butyl 2-(3-((methylsulfonyl)oxy)propyl)azepane-1-carboxylate, 14f**. *New product*. Mesylate **14f** was synthesized according to procedure F but with 0.80 g (3.11 mmol) of carbamate **14e**, 0.65 mL (0.47 g, 4.64 mmol, 1.5 equiv.) of triethylamine and 0.084 g (0.69 mmol, 0.22 equiv.) of *N*,*N*-dimethylaminopyridine (DMAP) and 0.36 mL (0.53 g, 4.66 mmol, 1.5 equiv.) of methanesulfonyl chloride. The organic phase was dried over $MgSO_4$ and concentrated to afford a crude reaction mixture (1.1 g) which was dissolved in 3 mL of diethyl ether and poured into a chromatographic column (30 × 2.5 cm, diethyl ether/petroleum ether 20:80) filled with 20 g of silica. The combined fractions were evaporated to afford 0.98 g (94%) of mesylate **14f** as a yellowish highly viscous oil. R_f = 0.6 (diethyl ether ether/petroleum ether, 80:20). ^{1}H NMR [$CDCl_3$, 300 MHz, 2 rotamers (65:45)] δ = 4.30–4.18 (m, 2 H), 4.15–4.04 (m, 0.65 H, br.), 3.96–3.86 (m, 0.45 H, br.), 3.72 (dm, *J* = 13.6 Hz, 0.45 H, br.), 3.60 (dm, *J* = 13.6 Hz, 0.65 H, br.), 3.00 (s, 3 H), 2.64 (tm, *J* = 13.6 Hz, 1 H), 2.11–1.97 (m, 1 H), 1.46 (s, 4 H), 1.45 (s, 5 H), 1.84–1.41 (m, 7 H), 1.26–1.14 (m, 4 H). ^{13}C{^{1}H} NMR [$CDCl_3$, 75 MHz, 2 rotamers (65:45), splitting signals are indicated with an asterisk (*)] δ = [156.7 (q), 155.7 (q)]*, [79.4 (s), 79.0 (s)]*, [70.4 (s), 70.0 (s)]*, [54.6 (t), 53.4 (t)]*, [41.6 (s), 41.4 (s)]*, [37.4 (p), 37.2 (p)]*, [35.0 (s), 34.7 (s)]*, [30.9 (s), 30.6 (s)]*, 29.8 (s), [28.6 (p), 28.5 (p)]*, [28.9 (s), 28.2 (s)]*, [26.1 (s), 26.0 (s)]*, [25.1 (s), 24.8 (s)]*. IR (film, cm^{-1}) 527, 1158, 1351, 1678, 2927. HRMS [ESI$^+$, CH_3OH/CH_2Cl_2 (90:10)] m/z: [M + Na]$^+$ Calcd for $C_{15}H_{29}NO_5NaS$ 358.1659; Found 358.1662.

3-(Azepan-2-yl)propyl methanesulfonate, hydrochloride salt, 15b•HCl. *New product*. Hydrochloride salt **15b•**HCl was synthesized according to procedure G but with 0.77 g (2.29 mmol) of mesylate **14f** to afford 0.50 g (80%) of hydrochloride salt **15b•**HCl as a white slightly hygroscopic solid. M.p. = 180–182 °C.[31] ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 9.25 (s, 1 H, br., 9.55 (s, 1 H, br.), 4.29 (s, 2 H, br.), 3.37–2.99 (m, 3 H), 3.07 (s, 3 H), 2.25–1.52 (m, 12 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ = 69.4 (s), 58.3 (t), 45.4 (s), 37.7 (p), 30.8 (s), 30.1 (s), 26.8 (s), 25.7 (s), 25.0 (s), 24.9 (s). IR (neat, cm^{-1}) 530, 948, 1164, 1354,

2754, 2927. HRMS [ESI$^+$, CH_2Cl_2/CH_3OH (90:10)] m/z: C^+ Calcd for $C_{15}H_{29}NO_5NaS$ 236.1315; Found 236.1318.

Octahydro-1*H*-pyrrolo[1,2-a]azepine, 3. To a solution of 0.25 g (0.91 mmol) of hydrochloride salt **15b•**HCl dissolved in 1 mL of water and cooled to 0 °C, was added 0.055 g (1.38 mmol, 1.5 equiv.) of powdered sodium hydroxide. The solution was stirred for 30 minutes upon which a pale oil gradually decanted. After a 12 h standing in an NMR tube, azepine **3** (0.095 g, 75%) was obtained as a colorless volatile oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 3.09–2.90 (m, 2 H), 2.42–2.22 (m, 3 H), 2.03–1.92 (m, 1 H), 1.86–1.37 (m, 11 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ = 65.5 (t), 57.8 (s), 55.6 (s), 34.9 (s), 33.6 (s), 28.2 (s), 26.3 (s), 26.0 (s), 22.9 (s). IR (neat, cm^{-1}) 913, 1164, 1634, 2931. HRMS [ESI$^+$, CH_2Cl_2/CH_3OH (90:10)] m/z: [M + H]$^+$ Calcd for $C_9H_{18}N$ 140.1434; Found 140.1434. Spectral data of compound **3** were in close agreement to those reported in ref.[10]

Octahydro-1H-pyrrolo[1,2-a]azepine, hydrochloride salt, 3•HCl. *New product*. Hydrochloride salt **3•**HCl has been synthesized according to procedure H to afford 0.12 g (76%) of hydrochloride salt **3•**HCl as a white solid. M.p. = 210 °C. ^{1}H NMR [$CDCl_3$, 300 MHz, 2 diastereoisomers (50:50)] δ = 4.05–3.87 (m, 1 H), 3.81–3.73 (m, 0.5 H), 3.67–3.57 (m, 0.5 H), 3.50–3.35 (m, 1 H), 3.08–2.80 (m, 2 H), 2.40–1.29 (m, 12 H). ^{13}C{^{1}H} NMR [$CDCl_3$, 75 MHz, 2 diastereoisomers (50:50)] δ = 67.6 (t), 65.7 (t), 57.1 (s), 56.6 (s), 54.9 (s), 52.6 (s), 33.2 (s), 32.5 (s), 30.5 (s), 29.8 (s), 28.9 (s), 27.6 (s), 25.6 (s), 25.1 (s), 24.3 (s), 24.0 (s), 22.2 (s). IR (neat, cm^{-1}) 1450, 2450, 2927. HRMS [ESI$^+$, CH_2Cl_2/CH_3OH (90:10)] m/z: C^+ Calcd for $C_9H_{18}N$ 140.1434; Found 140.1432.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information

Supporting Information Statement

Proton and carbon NMR spectra of derivatives **1**–**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

E-mail: jean-pierre.hurvois@univ-rennes1.fr

ORCID

Jean-Pierre Hurvois: 0000-0002-5728-8696

Christelle Bouvry : 0000-0003-0379-9762

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

C.B. would like to thank the Comprehensive Cancer Center Eugène Marquis for financial support. The author would also thank the members of the CRMPO (Centre Regional de Mesure Physique de l'Ouest) for technical assistance.

REFERENCES

[1] a) Wink, M.; In *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*; Fattorusso, E. Taglialatela-Scafati, O., Eds.; Wiley-VCH: Weinheim, 2007, pp. 1-24; (b) Roberts, M. F.; Strack, D.; In *Biochemistry of Plant Secondary Metabolism;* M. Wink, Ed.; Sheffield Academic Press, 1999, pp. 17–70.

[2] Aniszewski, T.; In *Alkaloids – Secrets of Life*; Elsevier: Amsterdam, 2007, pp. 1–315.

[3] Tamariz, J.; Burgueño-Tapia, E.; Vásquez, M. A.; Delgado F.; In *The alkaloids: Chemistry and Biology*; Knölker, H.-J. Ed.; Elsevier, **2018**, vol. 80, pp. 1–314.

[4] a) Zhang, J.; Morris-Natschke, S. L.; Ma, D.; Shang, X.-F.; Yang, C. J.; Liu, Y.-Q.; Lee, K.-H. Biologically active indolizidine alkaloids. *Med. Res. Rev*. **2021**, *41:2*, 928–960; b) Daly, J. W.; Spande T. F.; In *Alkaloids, Chemical and Biological Perspectives,* Vol. 4; S. W. Pelletier, Ed.; John Wiley & Sons, New-York, 1986, pp. 112–145; c) Elbein, A. D.; Molyneux, R. J.; In *Alkaloids, Chemical and Biological Perspectives,* Vol. 5; S. W. Pelletier, Ed.; John Wiley & Sons, New-York, 1987, pp. 1–49.

[5] For selected reviews, see: a) Asano, N.; Glycosidase inhibitors: update and perspectives on practical uses. *Glycobiology*, **2003**, *13:10*, 93R-104R; b) Borges de Melo, E.; da Silveira Gomes, A.; Carvalho, I. α- and β-Glucosidase inhibitors: chemical structure and biological activity. *Tetrahedron*, **2006**, *62*, 10277–10302.

[6] Yap, V. A.; Qazzaz, M. E.; Raja, V. J.; Bradshaw, T. D.; Loh, H.-S.; Sim, K.-S.; Yong, K.-T.; Low, Y.-Y.; Kim, K.-H. Fistulopines A and B, antiproliferative septicine-type alkaloids from *Fiscus fistulosa*. *Phytochem. Lett*. **2016**, *15*, 136-141.

[7] Daly, J. W.; Nishizawa, Y.; Padgett, W. L.; Tokuyama, T.; Smith, A. L.; Holmes, A. B.; Kibayashi, C.; Aronstam, R. S. 5,8-Disubstituted indolizidines: a new class of non-competitive blockers for nicotinic receptors-channels. *Neurochem. Res*. **1991**, *16:11*, 1213–1218.

[8] Garraffo, H. M.; Jain, P.; Spande, T. F.; Daly, J. W.; Jones, T. H.; Smith, L. J.; Zottig, V. E. Structure of alkaloid 275A, a novel 1-azabicyclo[5.3.0]decane from a dendrobatid frog, *Dendrobates lehmani*: synthesis of the tetrahydrodiastereomers. *J. Nat. Prod*. **2001**, *64*, 421–427.

[9] For a review on recent synthetic approaches, see: Jeon, H. Recent total syntheses of cephalotaxine-type alkaloids (2016-2021). *Asian J. Org. Chem*. **2021**, *10*, 3052–3067.

[10] Tehrani, K. A.; D'hooghe, M.; De Kimpe, N. Novel synthesis of indolizidine and quinolizidine. *Tetrahedron*, **2003**, *59*, 3099–3108.

[11] a) Kauloorkar, S. V.; Jha, V.; Kumar, P. Synthesis of indolizidine, pyrrolizidine and quinolizidine ring systems by proline-catalyzed sequential α-amination and HWE olefination of an aldehyde. *RSC Adv*. **2013**, *3*, 18288–18291; b) Kondekar, N. B.; Kumar, P. Synthesis of (*R*)-coniine and (*S*)-coinicine via organocatalytic α-aminoxylation of an aldehyde. *Synthesis*, **2010**, *18*, 3105–3112.

[12] Despinoy, X. L. M.; McNab, H. Hydrogenation of pyrrolizin-3-ones; new route to pyrrolizidines. *Org. Biomol. Chem*. **2009**, *7*, 4502–4511.

[13] Zimmer, R.; Collas, M.; Czerwonka, R.; Hain, U.; Reissig, H.-U. A new access to pyrrolizidine derivatives: ring contraction of methyl (*E*)-[1,2-oxazin-3-yl]propenoates. *Synthesis*, **2008**, *2*, 237–244.

[14] Kuhakarn, C.; Seehasombat, P.; Jaipetch, T.; Pohmakotr, M.; Reukratul, V. Synthesis of alkylated indolizidine alkaloids via Pummerer mediated cyclization: synthesis of (±)-indolizidine 167B, (±)-5-butylindolizidine and (±)-monomorine I. *Tetrahedon*, **2008**, *64*, 1663–1670.

[15] Reddy, B. V. S.; Chaya, D. N.; Yadav, J. S.; Grée, R. A concise diastereoselective synthesis of piperidine and indolizidine alkaloids via aza-Prins cyclization. *Synthesis*, **2012**, *44*, 297–303.

[16] Martín-López, M. J.; Rodriguez, R.; Bermejo, F. Decarbonylation of α-tertiary amino acids. Application to the synthesis of polyhydroxylated indolizidines from D,L-pipecolic acid. *Tetrahedron*, **1998**, *54*, 11623–11636.

[17] Kalaitzakis, D.; Triantafyllakis, M.; Sofiadis, M.; Noutsias, D.; Vassilikogiannakis, G. Photooxygenation of furylalkylamines: easy access to pyrrolizidine and indolizidine scaffold. *Angew. Chem. Int. Ed.* **2016**, *55*, 4605–4609.

[18] Kiewel, K.; Tallant, M.; Sulikowski, G. A. Asymetric Heck cyclization route to indolizidine and azaazulene alkaloids: synthesis of (+)-epiindolizidine 167B and indolizidine 223AB. *Tetrahedron Lett*. **2001**, *42*, 6621–6623.

[19] Quevedo-Acosta, Y.; Jurberg, I. D.; Gamba-Sánchez, D. Activating imides with triflic acid: a general intramolecular aldol condensation strategy toward indolizidine, quinolizidine, and valmerin alkaloids. *Org. Lett*. **2020**, *22*, 239–243.

[20] a) Illuminati, G.; Mandolini, L. Ring closure reaction of bifunctional chain molecules. *Acc. Chem. Res*. **1981**, *14*, 95–102; b) Galli, C.; Mandolini, L. The role of ring strain on the ease of ring closure of bifunctional chain molecules. *Eur. J. Org. Chem*. **2000**, 3117–3125.

[21] Reductive amination or RCM reaction: Fayedi, O. O.; Senter, T. J.; Hahn, K. N.; Lindsley, C. W. A versatile enantioselective synthesis of azabicyclic ring systems: a concise total synthesis of (+)-grandisine D and unnatural analogues. *Chem. Eur. J*. **2012**, *18*, 5826–5831.

[22] a) Olfson, R. M.; Gadallah, F. F.; Laidler, J. K. Bicyclization of aza-compounds by positive halide ions I. Cyclic amines. *Can. J. Chem*. **1985**, *63*, 1170–1172; b) Schell, F. M.; Ganguly, R. N. Silver ion induced rearrangement of *N*-chloramines. Isolation of an ionic product in high yield. *J. Org. Chem*. **1980**, *45*, 4069–4070.

[23] Hammond, G.B.; Plevey, R. G. New synthesis of 1-azabicyclo[5.3.0]decane. *Org. Prep. Proced. Int*. **1991**, *23:6*, 735–739.

[24] Patterson, J. M.; Soedigo, S. Pyrrolysis products of cycloalkano|a] pyrroles. *J. Org. Chem*. **1967**, *32*, 2969–2971.

[25] Bouvry, C.; Franzetti, M.; Cupif, J.-F.; Hurvois, J.-P. Total synthesis of phenanthropiperidine alkaloids by sequential alkylation of *N*,*N*-dibenzylaminoacetonitrile. *Eur. J. Org. Chem*. **2021**, 6037–6051.

[26] For reviews on the formation and chemistry of metalated α-aminonitriles, see: a) Opatz, T. The chemistry of deprotonates α-aminonitriles. *Synthesis* **2009**, *12*, 1941–1959; b) Enders, D.; Shilvock, J. P. Some recent applications in α-amino nitrile chemistry. *Chem. Soc. Rev*. **2000**, *29*, 359–373.

[27] For previous utilizations of lithiated α-aminonitrile **4** in synthesis, see: a) Leclerc, E.; Vrancken, E.; Mangeney, P. Diastereoselective aldolization of α-aminonitriles. Diastereoselective synthesis of β-amino alcohols and β,γ-diamino alcohols. *J. Org. Chem*. **2002**, *67*, 8928–8937; c) Bahde, R. J.; Rychnovsky, S. D. Cyclization via carbolithiation of α-amino alkyllithium reagents. *Org. Lett.* **2008**, *10*, 4017–4020.

[28] See also: Ogura, K.; Shimamura, Y.; Fujita, M. Reductive decyanization of α-amino nitriles by borane. *J. Org. Chem*. **1991**, *56*, 2920–2922.

[29] Kim, Y. H.; Choi, J. Y. Diastereoselective addition of organolithiums to new chiral hydrazones. Enantioselective synthesis of (*R*)-coniine. *Tetrahedron Lett*. **1996**, *37*, 5543–5546.

[30] Baldwin, J. E. Rules for ring closure. *J. Chem. Soc. Chem. Commun*. **1976**, *18*, 734–736.

[31] Due to a rapid decomposition on the hot bench, the melting points of hydrochloride salts **13a-c** and **15b** were reported for guidance.

[32] To the best of our knowledge, spectral data of hydrochloride **13a-c** have not been reported in the literature.

[33] a) Vaquero, J. J.; Cuadro, A. M.; Herradón, B. In *Modern Heterocyclic Chemistry*; Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J.; Eds.; Wiley-VCH: Weinheim, 2011, pp. 1865–1988; b) Meyer, A. G.; Bissember, A. C.; Hyland, C. J. T.; Williams, C. C.; Szabo, M.; Pearsall, M. A.; Hyland, I. K.; Olivier, W. J.; In *Progress in Heterocyclic Chemistry*; Gribble, G. W.; Joule, J. A.; Eds.; Elsevier, 2020, *31*, pp. 597–647.

[34] Deng, H.-Q.; Qian, X.-Y.; Li, Y.-X.; Zheng, J.-F.; Xie, L.; Huang, P.-Q. A versatile two-step method for the reductive alkylation and formal [4 + 2] annulation of secondary lactams: step economical syntheses of the ant venom alkaloids (2*R*,2*S*)-2-butyl-5-propylpyrrolidine and (+)-monomorine I. *Org. Chem. Front*. **2014**, *1*, 258-266.

[35] Tran, H. V.; Vu, H.-D.; Graton, J.; Jacquemin, D.; Renault, J.; Uriac, P. Synthesis of heterocyclic enamine-zinc complexes as precursors of stereocontrolled substitution of nitrogen α-position. *Tetrahedron Lett*. **2020**, *61*, 152405.

[36] Thomson, A. M.; Delanay, A. M.; Hamby, J. M. H.; Schroeder, M. C.; Spoon, T. A.; Crean, S. M.; Showalter, H. D. H.; Denny, W. A. Synthesis and structure–activity relationships of soluble 7-sustituted 3-(3,5-dimethoxyphenyl)-1,6-naphtyridin-2-amines and related ureas as dual inhibitors of the fibroblast growth inhibitor-1 and vascular endothelial growth factor receptor-2 tyrosine kinase. *J. Med. Chem*. **2005**, *48*, 4628–4653.

[37] Arian, D.; Kovbasyuk, L, Mokhir, A. 1,9-dialkoxyanthracene as a $^1O_2$-sensitive linker. *J. Am.* Chem. Soc. **2011**, *133*, 3972–3980.

[38] Gorske, B. C.; Mbofana, C. T.; Miller, S. J. Regio- and stereoselective synthesis of fluoroalkenes by direct Au(I) catalysis. *Org. Lett.* **2009**, *11*, 4318–4321.

[39] Van de Sande, M.; Gais, H.-J. Asymmetric synthesis of 3-oxa-15deoxy-16-(*m*-tolyl)-17,18,19,20-tetranorisocarbacyclin and its neuroprotective analogue 15-deoxy-16-(m-tolyl-17,18,19,20-tetranorisocarbacyclin based on the conjugate addition-azoalkene-asymmetric olefination strategy. *Chem. Eur. J*. **2007**, *13*, 1784–1795.

[40] Guan, J.; Kyle, D. E.; Gerena, L.; Zhang, Q.; Milhous, W. K.; Lin, A. J. Design, synthesis and evaluation of new chemosensitizers in multi-drug-resistant *Plasmodium falciparu*m. *J. Med. Chem*. **2002**, *45*, 2741–2748.

[41] Li, W.-S.; Kuo, T.-S.; Hsieh, M.-C.; Tsai, M.-K.; Wu, P.-Y.; Wu, H.-L. Enantioselective rhodium-catalyzed allylation of aliphatic imines: synthesis of chiral C-aliphatic homoallylic amines. *Org.Lett*. **2020**, *22*, 5675–5679.

[42] Kamijo, S.; Kamijo, K.; Maruoka, K.; Murafuji, T. Aryl ketone catalyzed radical allylation of C(sp^3)-H under photoirradiation. *Org. Lett*. **2016**, *18*, 6516–6519.

[43] Nebe, M. M.; Zinn, S.; Opatz, T. A short and modular approach towards 3,5-disubstituted indolizidine alkaloids. *Org. Biomol. Chem*. **2016**, *14*, 7084–7091.