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A New and Efficient Synthesis of Derivatives of Octahydro-4*H*-pyrrolo-[1,2-*c*]pyrido[1′,2′-*a*]imidazole

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When diethyl malonate was added to a solution of Δ^1-piperideine, generated in situ by oxidative desamination and decarboxylation of L-lysine by *N*-bromosuccinimide (NBS), formation of the unexpected tricyclic compound **6** (4-diethylmalonyl-octahydro-4*H*-pyrrolo[1,2-*c*]pyrido[1′,2′-*a*]imidazole) was observed. The structure of **6** was deduced from analysis of its spectroscopic data and was confirmed both by chemical degradation and by total synthesis. We proved that 3-bromo-1-piperideine was implicated in its formation. Moreover, based on this feature, a new and efficient synthesis of **6** was developed. The elaborated pathway was adapted to access derivatives related to **6** that differed in their C-4 substituent.

Introduction

Pseudomyrmecine ants of the genus *Tetraponera* utilize their modified sting to smear upon enemies a contact poison that contains a mixture of tricyclic alkaloids.[1–3] These alkaloids, named tetraponerines, can be distributed into two structural families, which are based either on the decahydrodipyrrolo[1,2-*a*:1′,2′-*c*]pyrimidine skeleton (**1**; 5-6-5 skeleton) or on the decahydro-5*H*-pyrido[1,2-*c*]pyrrolo-[1′,2′-*a*]pyrimidine skeleton (**2**; 6-6-5 skeleton) (Figure 1).

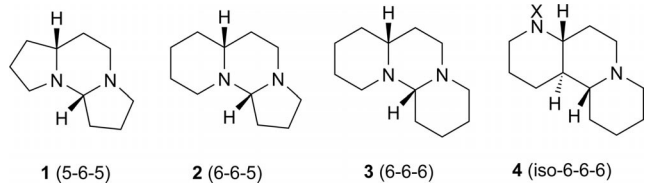

Figure 1. Tetraponera alkaloid skeletons (**1** and **2**) and synthetic analogues (**3** and **4**).

In the framework of a program focused on the search for bioactive compounds in insects, preliminary tests indicated that the tetraponerines presented interesting cytotoxic activities. It has also been shown that these molecules possess neurotoxic[4] and insecticidal activities.[1] To evaluate the influence of the tricyclic ring system on the cytotoxic activity, we have recently described the synthesis of a series of non-natural tricyclic alkaloids based on the skeletons decahydro-2*H*,6*H*-dipyrido[1,2-*a*:1′,2′-*c*]pyrimidine (**3**; 6-6-6 skeleton) and dodecahydro-2*H*-1,8a-diazaphenanthrene (**4**; iso-6-6-6 skeleton) (Figure 1).[5] Δ^1-Piperideine (**5**), which is an unstable imine that must be prepared in situ, was used as starting material to perform these syntheses. We found that the best yields of the target intermediates were obtained by generation of **5** by slow detrimerization of α-tripiperideine. In this paper, we wish to report the unexpected results we have obtained on generation of Δ^1-piperideine using the reaction of lysine with *N*-bromosuccinimide (NBS).[6,7]

Results and Discussion

Franck and Randau[8] have demonstrated that at pH 3 or lower, the reaction of NBS with amino acids provides, by oxidative desamination and decarboxylation, the corresponding aldehyde with one carbon less. Under these conditions, L-lysine is transformed into 5-aminopentanal, which cyclizes spontaneously into Δ^1-piperideine.[8] When we treated a solution of Δ^1-piperideine, prepared according to this method, with diethyl malonate (DEM) in the hope of forming 6-6-6 or iso-6-6-6 intermediates as described previously,[5] we observed consistent formation of the unexpected tricyclic product **6** (5-5-6 skeleton) in moderate yields (best yield 26%) together with polymeric material. Despite numerous assays, which were carried out at various pH and various proportions of reactants, we never isolated 6-6-6 or iso-6-6-6 derivatives under these conditions.

The molecular formula of compound **6** was established to be $C_{17}H_{28}N_2O_4$ (M^+ at *m/z* 324.2033) by HRMS (EI), requiring five double bond equivalents. The IR, ^1H, and ^{13}C NMR spectra indicated the presence of two ethyl ester groups and, because no further signals attributable to sp^2 carbon atoms were observed, it was reasonable to assume that **6** must be tricyclic. Moreover, because no ν_{NH} absorption was present in the IR spectrum, the two nitrogen atoms must be tertiary. A detailed analysis of the 1D and 2D NMR spectra (^1H–^1H COSY, HMQC, and HMBC) led to the atom connectivity depicted in **6** and permitted the com-

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plete NMR assignments reported in the experimental part. The relative configurations at C-3a, C-4, and C-9a were deduced by a NOESY experiment. Indeed, NOE correlations between H-6α/H-1′, H-9a/H-4, H-9a/H-1β, H-9a/H-6β, H-4/H-3β, and H-4/H-6β suggested that H-9a and H-4 are *cis*-oriented and that cycles A/B and B/C are *cis*- and *trans*-fused, respectively (Figure 2). Until now, the only known compound having a 5-5-6 skeleton similar to that of compound **6** is (–)-dysibetaine PP (**7**), an amino acid derivative isolated from the marine sponge *Dysidea herbacea*.[9] Compound **7** has been synthesized starting from a dipeptide in a six-step synthesis.[10] It should be noted that the relative configuration of **6** is different to that of the natural product **7**.

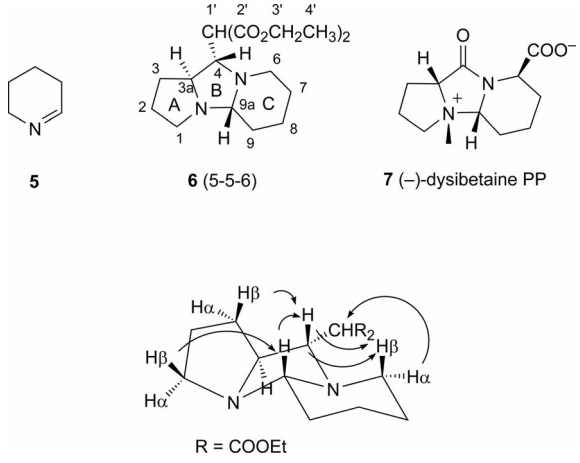
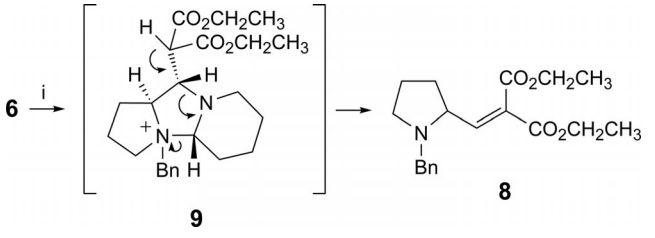


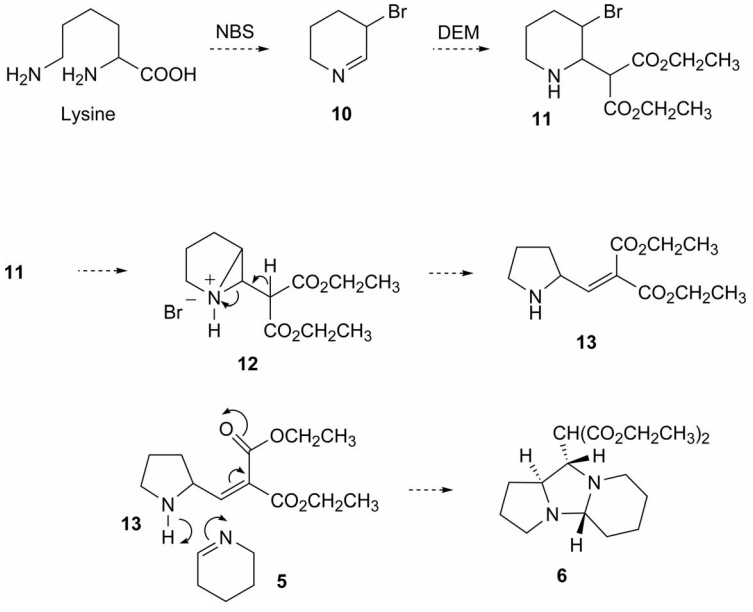
Figure 2. Structure of starting Δ^1-piperideine (**5**), the product **6**, NOE correlations, and the natural product (–)-dysibetaine PP (**7**).

The structure deduced from analysis of the spectroscopic data of **6** was confirmed both by chemical degradation and by synthesis. Thus, when compound **6** was treated with one equivalent of benzyl bromide or benzyl chloride in $CHCl_3$ at room temperature to prepare a quaternary salt, which was more likely than the free base to lead to a crystalline solid for X-ray analysis, the 2-substituted pyrrolidine **8** was isolated as the major product (ca. 49% yield). Formation of the latter can be explained by assuming that the intermediate quaternary salt **9** undergoes a reverse Michael-type reaction with elimination of a molecule of Δ^1-piperideine and of HBr (Scheme 1).



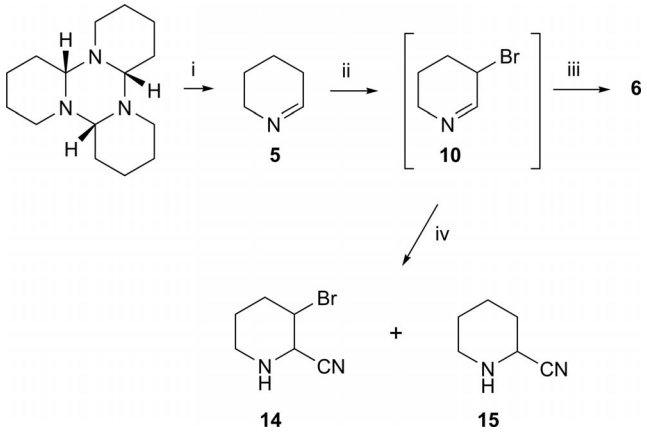
Scheme 1. Chemical degradation of **6**. Reagents and conditions: (i) $PhCH_2Br$ or $PhCH_2Cl$, $CHCl_3$, room temp., 4 h, 52% and 44%, respectively.

A plausible mechanism for the generation of **6** using the NBS/lysine procedure is outlined in Scheme 2. The pathway involves the formation of 3-bromo-1-piperideine (**10**) resulting from the bromination of **5** in the presence of an excess of NBS. It is well-known that treatment of aldimines with NBS or NCS yields the corresponding α-bromoaldimines or α-chloroaldimines, respectively.[11,12] After addition of diethyl malonate to the imino group, the resulting 3-bromopiperidine **11** could undergo internal substitution of the bromine, leading to the aziridinium ion **12**.[13] Subsequent opening of the aziridinium ring and elimination of HBr would then afford pyrrolidine **13**. Finally, a Michael-type reaction between the latter and a second molecule of **5** would provide compound **6**.



Scheme 2. Proposed pathway for the formation of **6**.

To support our hypothesis, we verified that by treating Δ^1-piperideine (**5**) with NBS, the proposed intermediate **10** could indeed be produced. Thus, to an aqueous solution of **5**, prepared by detrimerization of α-tripiperideine in HCl, one equivalent of NBS was added followed by addition of KCN to trap the unstable imine **10** that was expected to be formed during the reaction. Analysis and purification of the resulting solution led to the isolation of 3-bromo-2-cyanopiperidine (**14**) in 6% yield, together with 2-cyanopiperidine (**15**) in 33% yield. Moreover, when KCN was replaced by diethyl malonate to trap the elusive imino intermediate, compound **6** was isolated, albeit in low yield (10%). This indicated that **10** is indeed generated under these conditions (Scheme 3). The yields of these reactions were not optimized.



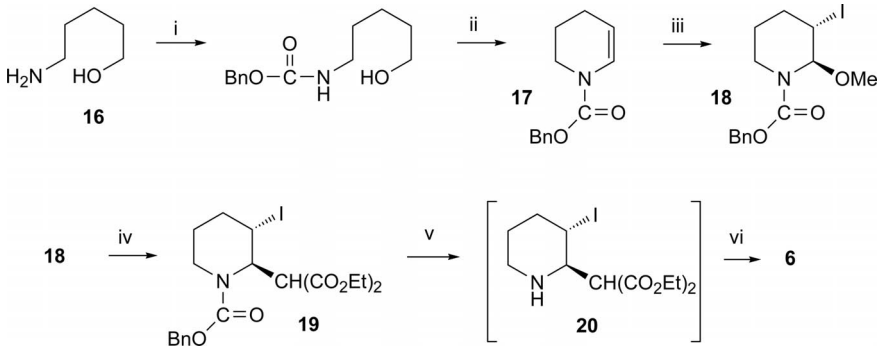
Scheme 3. Proof of the intermediate formation of 3-bromo-1-piperideine (**10**). Reagents and conditions: (i) HCl (1 N), 10 min, 20 °C, then NaOH → pH = 2; (ii) NBS, 20 min, 45 °C; (iii) NaOH → pH = 6, then DEM, 17 h, room temp., 10%; (iv) NaOH → 2 < pH < 3, then KCN, 3 h, 20 °C, **14** (6%) and **15** (33%).

Additional proof for the structure of **6** was obtained by its synthesis using a pathway based on the hypothesis that a 3-halopiperidine was involved in its formation (Scheme 4). The first step was the preparation of iodopiperidine **18** starting from 5-amino-1-pentanol (**16**). The second step was the generation, after deprotection of the amino group, of the tricyclic 5-5-6 system by subsequent treatment with Δ^1-piperideine (**5**). To perform this synthesis, we decided to use NIS instead of NBS because we expected better yields for the introduction of the halogen at position C-3 of the piperidine ring, as well as for the formation of the aziridinium intermediate. The intermediate **18** was easily prepared from the commercially available amino alcohol **16** as shown in Scheme 4. Accordingly, successive protection of the primary amine, oxidation of the hydroxyl group to an aldehyde, and spontaneous cyclization produced the protected Δ^2-piperideine **17**; subsequent treatment with NIS/MeOH afforded the *trans*-2-methoxy-3-iodopiperidine **18**.[14] The next step was the introduction of the diethyl malonyl group in the form of a titanium enol ether, which was prepared in situ using a mixture of $TiCl_4$ and *N*,*N*-diisopropylethylamine (DIPEA).[15–17] The key compound **19** was obtained through this approach in an overall yield of 63% from **16**. Only the *trans* diastereoisomer was isolated. This high stereoselectivity resulted from the introduction of the diethyl malonyl group as an iminium ion, which directed the nucleophilic attack in an *anti* fashion.

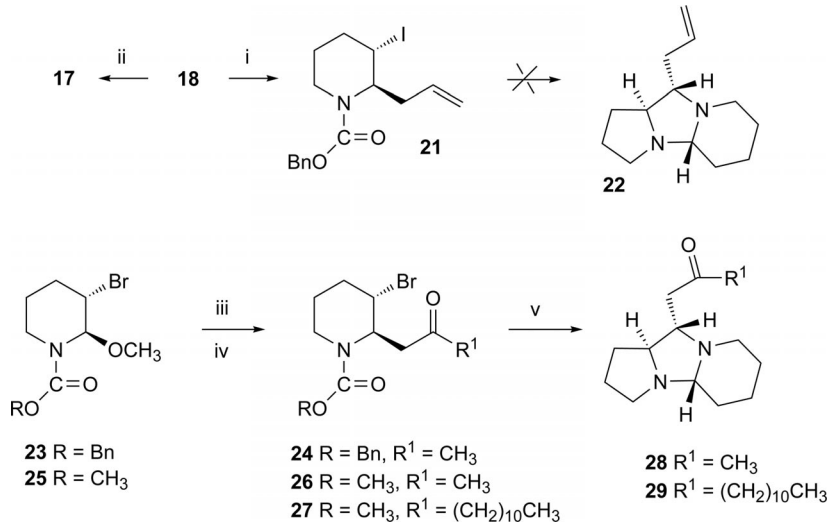
After deprotection of the secondary amino group of **19** with trimethylsilyl iodide (TMSI) in acetonitrile and concentration of the solution under reduced pressure, the resulting *N*-silylpiperidine intermediate was hydrolyzed with aqueous HCl (10%), affording the corresponding secondary amine **20**, which was not isolated. Ground α-tripiperideine was added and the pH was raised to 2.5 by cautious addition of KOH (2 M). After 16 h at room temperature and work up of the mixture, compound **6** was isolated in 67% yield after purification by column chromatography on silica gel. It is notable that no other diastereoisomers of **6** were isolated, suggesting that the Michael-type cyclization also proceeds with high stereoselectivity.

These data are consistent with the structure proposed for **6**, as well as with the involvement of a 3-halopiperidinic intermediate in its formation when NBS/lysine is used to generate the unstable Δ^1-piperideine **5** in situ.

At this stage of the work, the next problem we addressed was the use of intermediate **18** to reach 5-5-6 derivatives that differed at their C-4 substituent. To this end, several



Scheme 4. Total synthesis of **6**. Reagents and conditions: (i) $ClCO_2Bn$, K_2CO_3, $EtOH/H_2O$, 0 °C to room temp., 3 h, 89%; (ii) PCC/SiO_2, CH_2Cl_2, ultrasound, 1 h, 88%; (iii) NIS, CH_2Cl_2/MeOH, 0 °C to room temp., 16 h, 87%; (iv) (a) DEM, $TiCl_4$, CH_2Cl_2, 0 °C, 5 min; (b) DIPEA, 0 °C, 1 h, (c) **18**, –6 °C, 1 h, 93%; (v) TMSI, CH_3CN, 0 °C to room temp., 19 h; (vi) (a) HCl (10%); (b) α-tripiperideine, KOH (2 M) → pH = 2–3, room temp., 16 h, 67%.



Scheme 5. Synthesis of analogues of **6**. Reagents and conditions: (i) CH_2=$CHCH_2SiMe_3$, BF_3·OEt_2, CH_2Cl_2, –78 °C, 2 h, 52%; (ii) $TiCl_4$, CH_2Cl_2, isopropenyl acetate, –78 °C, 1 h, 40%; (iii) $TiCl_4$, CH_2Cl_2, isopropenyl acetate, –78 °C, 1 h, then –78 °C to room temp., 16 h, **24** (19%) and **26** (77%); (iv) same conditions as for (iii), 2-(trimethylsilyloxy)-1-dodecene, **27** (60%); (v) (a) **28**: TMSI, CH_3CN, 20 °C, 16 h; **29**: TMSI, $CHCl_3$, reflux, 24 h; (b) HCl (10%); (c) α-tripiperideine, KOH (2 M) → pH = 2–3, room temp., 16 h, **28** (61%) and **29** (54%).

nucleophiles and experimental conditions were tested. It appeared that treatment of **18** with allylmethylsilane/Et_2O·BF_3 readily afforded piperidine **21**, whereas treatment with isopropenylacetate/$TiCl_4$ or 2-(trimethylsilyloxy)propene[18]/$TiCl_4$[14,15,17,19–21] did not lead to substitution of the methoxy group by an acetonyl moiety (Scheme 5). Under these latter conditions, only the Δ^2-piperideine **17** was isolated in 40% yield. This was attributed to the weakness of the C–I bond, which can be cleaved in the presence of Lewis acid such as $TiCl_4$ or trimethylsilyl trifluoromethanesulfonate (TMSOTf).[22] Indeed, when the corresponding bromine derivative **23** was submitted to the same conditions, the expected acetonyl derivative **24** was formed albeit in low yield (18%). A much better yield (77%) was nevertheless obtained when the benzyloxycarbonyl protecting group was replaced by a methoxycarbonyl group.

In our previous paper, we reported that analogues of tetraponerines with long *n*-alkyl substituents have higher cytotoxicity. Therefore, for comparison purposes, we synthesized the 4-*n*-dodecane-substituted 5-5-6 analogue **29**. Similar to the preparation of **26** from **25**, compound **27** was prepared in 60% yield from **25** using 2-(trimethylsilyloxy)-1-dodecene[18]/$TiCl_4$ as reagent (Scheme 5). The bromine derivatives **23** and **25** where prepared following the pathway depicted in Scheme 4, but NIS was replaced by NBS and, for compound **25**, methyl chloroformate was used instead of benzyl chloroformate to protect the amino group.

Deprotection of the secondary amine of **26** and **27** by treatment with TMSI/CH_3CN (for **26**) and TMSI/$CHCl_3$ (for **27**) followed by successive addition of aqueous HCl (10%) and ground α-tripiperideine, afforded the tricyclic compounds **28** (61% yield) and **29** (54% yield), respectively.

It is to be noted that when **21** was submitted to the same reaction sequence, no cyclization occurred and compound **22** was not formed, probably because the Michael-like reaction could not take place owing to the reduced acidity of the allylic proton H-1′ of **21**.

In conclusion, the serendipitous finding that Δ^1-piperideine (**5**), generated using the lysine/NBS mixture, reacts with diethyl malonate to afford the tricyclic derivative **6** following a pathway involving a 3-halopiperideine intermediate, led us to develop a new and efficient way to reach derivatives of octahydro-4*H*-pyrrolo[1,2-*c*]pyrido[1′,2′-*a*]imidazole, a seldom encountered heterocycle, with high stereoselectivity.

Experimental Section

General: Unless otherwise noted, materials were obtained from Aldrich or Acros and were used without purification. Diethyl ether was distilled from Na-benzophenone ketyl or $LiAlH_4$ prior to use. Dichloromethane and acetonitrile were distilled prior use from P_2O_5 or CaH_2. Chloroform was distilled from P_2O_5. Piperidine, diisopropylamine, diisopropylethylamine, and triethylamine were freshly distilled from CaH_2. MeOH and EtOH were dried and distilled from CaH_2. All reactions were carried out under an atmosphere of dry nitrogen. α-Tripiperideine was prepared by reaction of piperidine with NCS, followed by dehydrohalogenation of *N*-chloropiperidine with KOH in boiling ethanol.[23,24]

EI-MS and HRMS (EI) were performed with a Fisons VG Micromass Autospec instrument (70 eV). HRMS (ES) were performed with a Waters Q-TOF 2 instrument in positive ionization mode. In all cases, peak intensities are expressed as a percentage relative to the base peak. The ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 MHz with a Bruker Avance TM 300 or at 600 MHz with a Varian Unity 600 instrument and are reported in ppm from internal TMS on the δ scale. Data are reported as follows: chemical shift [multiplicity (s: singlet, d: doublet, dd: double doublet, ddd: double double doublet, t: triplet, dt: double triplet, tt: triple triplet, q: quartet, m: multiplet), coupling constants in Hertz, integration]. The ^{13}C NMR spectra were recorded in $CDCl_3$ at 75.4 MHz with

a Bruker Avance TM 300 instrument. The IR spectra were recorded with a Bruker IFS 25 instrument as films on a NaCl disk. Thin layer chromatographic analyses (TLC) were performed with 0.25 mm Polygram silica gel SILG/UV254 precoated plates (Macherey–Nagel). Chromatographic separations were performed with silica gel columns (MN Kieselgel 60, 0.04–0.063 mm) using the flash technique or on basic alumina (MN Aluminiumoxid, basisch Activity 1).

4-(Diethylmalonyl)-octahydro-4*H*-pyrrolo[1,2-*c*]pyrido[1′,2′-*a*]imidazole (6): NBS (572 mg, 3.21 mmol) was added to a solution of L-lysine monohydrochloride (293 mg, 1.60 mmol) in water (20 mL). The solution was kept at 45 °C for 20 min. Gentle suction was applied to remove bromine vapors (pH of the solution: ca. 1.6). Aqueous KOH (1 M) was added dropwise at 0 °C until pH 6.5 was reached. Then, diethyl malonate (243 μL, 1.6 mmol) was poured into the solution in one portion. After stirring overnight under nitrogen at room temp., the pH (ca. 3.6) was brought to pH 8 with KOH (1 M) and the solution was extracted with CH_2Cl_2. The combined organic phases were dried and the solvent was removed by evaporation in vacuo to give a crude product that was purified by flash chromatography on silica gel (CH_2Cl_2/CH_3OH/NH_4OH 10%, 99:1:0.1) to afford compound **6** (68.5 mg, 0.21 mmol, 26%). IR (NaCl disc): $\tilde{\nu}_{max}$ = 2939, 2861, 2800, 1730, 1448, 1369, 1274, 1175, 1152, 1032 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 1.24 (m, 1 H, 8-H_α), 1.29 (t, J = 7.2 Hz, 6 H, 4′-H_3), 1.45 (qt, J = 12.6, 3.6 Hz, 1 H, 7-H_α), 1.60 (m, 2 H, 9-H_α, 7-H_β), 1.77 (m, 1 H, 3-H_α), 1.82 (br. d, J = 13.8 Hz, 1 H, 8-H_β), 1.85 (m, 1 H, 2-H_β), 1.90 (m, 2 H, 2-H_α, 9-H_β), 2.03 (m, 1 H, 3-H_β), 2.08 (td, J = 12, 2.4 Hz, 1 H, 6-H_α), 2.72 (br. d, J = 9 Hz, 1 H, 9a-H_α), 2.79 (m, 1 H, 1-H_α), 2.90 (t, J = 6 Hz, 1 H, 4-H_α), 3.02 (br. d, J = 10.8 Hz, 1 H, 6-H_β), 3.12 (br. s, 1 H, 1-H_β), 3.71 (d, J = 5.4 Hz, 1 H, 1′-H), 4.00 (br. s, 1 H, 3a-H_α), 4.25 (m, 4 H, 3′-H_2) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ = 14.1, 14.2 (C-4′), 22.8 (C-8), 24.9 (C-7), 25.3 (C-2), 30.7 (C-9), 31.2 (C-3), 49.9 (C-6), 50.9 (C-1), 53.6 (C-1′), 61.5, 61.6 (C-3′), 65.5 (C-3a), 67.8 (C-4), 85.6 (C-9a), 167.6, 168 (C-2′) ppm. HRMS (EI): m/z = 324.2033 (calcd. for $C_{17}H_{28}N_2O_4$: 324.2049), 323.1968 (calcd. for $C_{17}H_{27}N_2O_4$ 323.1971), 296.1733 (calcd. for $C_{15}H_{24}N_2O_4$ 296.1736), 255.1460 (calcd. for $C_{13}H_{21}NO_4$ 255.1471), 251.1754 (calcd. for $C_{14}H_{23}N_2O_2$ 251.1760), 223.1452 (calcd. for $C_{12}H_{19}N_2O_2$ 223.1447), 182.1192 (calcd. for $C_{10}H_{16}NO_2$ 182.1181), 165.1516 (calcd. for $C_{11}H_{19}N$ 165.1518).

1-Benzyl-2-[2-bis(ethoxycarbonyl)vinyl]pyrrolidine (8): Benzyl bromide (19 μL, 0.16 mmol) was added dropwise to a stirred solution of **6** (50 mg, 0.15 mmol) in anhydrous chloroform (1 mL) under nitrogen. After 4 h at room temp., an aqueous solution of $NaHCO_3$ was added. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried and evaporated under reduced pressure. Flash chromatography on silica gel of the solid residue (CH_2Cl_2/MeOH/NH_4OH 10%, 99:1:0.1) yielded **8** (27 mg, 0.080 mmol, 52%) as a colorless oil and unreacted **6** (8 mg, 0.024 mmol, 15%). The use of benzyl chloride instead of benzyl bromide under the same conditions afforded **8** with a yield of 44%. IR (NaCl disc): $\tilde{\nu}_{max}$ = 3089, 3062, 3028, 2981, 2940, 2876, 2802, 1729, 1650, 1452, 1368, 1246, 1213, 1182, 1054 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.2 Hz, 3 H, 9′-H), 1.34 (t, J = 6.6 Hz, 3 H, 9-H), 1.72 (m, 2 H, 2-H, 3-H), 1.85 (m, 1 H, 3-H), 2.05 (m, 1 H, 2-H), 2.21 (q, J = 9 Hz, 1 H, 4-H), 2.99 (br. t, J = 7 Hz, 1 H, 4-H), 3.24 [d, J = 13.2 Hz, 1 H, CH_2(Bn)], 3.29 (m, 1 H, 1-H), 3.93 [d, J = 13.2 Hz, 1 H, CH_2(Bn)], 4.23 (q, J = 7.2 Hz, 2 H, 8′-H), 4.30 (q, J = 6.6 Hz, 2 H, 8-H), 6.94 (d, J = 9.6 Hz, 1 H, 5-H), 7.23 (m, 1 H, Ar-H), 7.29 (m, 4 H, Ar-H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ = 14.2, 14.3 (C-9, C-9′), 23.0 (C-3), 31.3 (C-2), 53.6 (C-4), 58.9 (C-1′), 61.5 (C-8, C-8′), 63.4 (C-1), 127.1, 128.3, 129.1 (C-Ar), 129.2 (C-6), 138.9 (C-Ar), 151.1 (C-5), 163.8 (C-7′), 165.6 (C-7) ppm. HRMS (EI): m/z = 331.1767 (calcd. for $C_{19}H_{25}NO_4$ 331.1783), 286.1447 (calcd. for $C_{17}H_{20}NO_3$ 286.1443), 285.1369 (calcd. for $C_{17}H_{19}NO_3$ 285.1365), 258.1510 (calcd. for $C_{16}H_{20}NO_2$ 258.1494), 240.1250 (calcd. for $C_{12}H_{18}NO_4$ 240.1236), 194.0835 (calcd. for $C_{10}H_{12}NO_3$ 194.0817), 184.1116 (calcd. for $C_{13}H_{14}N$ 184.1126), 91.0546 (calcd. for C_7H_7 91.0546).

3-Bromo-2-cyanopiperidine (14): A solution of α-tripiperideine (0.146 g, 0.59 mmol) in aqueous HCl (1 M, 3 mL) was stirred for 10 min at room temp., then NaOH (1 M) was added dropwise until pH 1.9 was reached, then NBS (313 mg, 1.76 mmol) was added. The resulting solution was warmed to 45 °C while gentle suction was applied. After 20 min, the pH was brought to 1.9 by addition of NaOH (1 M) and KCN (149 mg, 2.29 mmol) was added. The pH of the mixture was maintained between 2 and 3 by regular addition of aqueous HCl (1 M). The mixture was stirred for 3 h at room temp., then basified to pH 8 by addition of NH_4OH and extracted with CH_2Cl_2. The combined organic phases were dried and the solvents evaporated in vacuo to dryness to give an oil, which was flash purified by chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + 1% concd. NH_4OH) to afford **14** (20 mg, 0.10 mmol, 6%) as a colorless oil, and 2-cyanopiperidine (64 mg, 0.59 mmol, 33%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50–2.00 (m, 3 H, 5-H_2, 4-H_{ax}), 2.37 (m, 1 H, 4-H_{eq}), 2.83 (m, 1 H, 6-H_{ax}), 3.07 (m, 1 H, 6-H_{eq}), 3.97 (d, J = 6.3 Hz, 1 H, 2-H), 4.21 (m, 1 H, 3-H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ = 24.1 (C-5), 32.7 (C-4), 43.8 (C-6), 47.8 (C-2), 54.3 (C-3), 115.6 (CN) ppm MS (EI): m/z (%) = 190 (7) $[M(Br^{81})]^+$, 188 (7) $[M(Br^{79})]^+$, 164 (7) $[M^{+\cdot}(Br^{81}) - CN^\cdot]$, 162 (7) $[M^{+\cdot}(Br^{79}) - CN^\cdot]$, 109 (100) $[M^+ - Br]$, 93 (20), 82 (42), 67 (49), 55 (45).

Formation of 6 from α-Tripiperideine: A solution of α-tripiperideine (142 mg, 0.57 mmol) in aqueous HCl (1 M, 2 mL) was stirred for 10 min at 20 °C under nitrogen. The pH was brought to 1.9 by addition of NaOH (1 M), then NBS (304 mg, 1.7 mmol) was added and the solution was stirred under nitrogen for 1 h at room temp. The pH was raised to 6 by addition of a solution of NaOH (1 M), and diethyl malonate (259 μL, 1.71 mmol) was added. After stirring overnight at room temp. under nitrogen, the pH was brought to 8 by addition of concd. NH_4OH. The solution was extracted with CH_2Cl_2 (3 × 20 mL), and the organic phases were combined, dried (WA filter paper), and the solvents evaporated under vacuum. Flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH 10%, 99:1:0.1) of the yellow oily residue afforded **6** (55.4 mg, 0.17 mmol, 10%).

5-(Benzyloxycarbonylamino)pentanol: A solution of K_2CO_3 (4.1 g, 29.6 mmol) in water (20 mL) was added to a solution of 5-amino-1-pentanol (1.57 mL, 14.5 mmol) in ethanol (20 mL). The reaction mixture was cooled in an ice-bath and benzyl chloroformate (2.7 mL, 18.9 mmol) was added under vigorous stirring. The ice-bath was maintained during 30 min and the mixture was warmed progressively to room temp. After 3 h, the mixture was extracted with CH_2Cl_2 and the combined organic layers were filtered through a WA filter paper and the solvent was evaporated in vacuo to give a residue that was purified by flash chromatography on silica gel (hexane/AcOEt, 5:5) to afford 5-(benzyloxycarbonylamino)pentanol (3.015 g, 12.7 mmol, 89%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.40 (m, 2 H, 3-H), 1.55 (m, 4 H, 2-H, 4-H), 3.20 (t, J = 6.7 Hz, 2 H, 5-H), 3.63 (t, J = 6.3 Hz, 2 H, 1-H), 5.09 (s, 2 H, CH_2Ph), 7.35 (m, 5 H, Ar-H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ = 22.9 (C-3), 29.9 (C-4), 32.3 (C-2), 41.1 (C-5), 62.8 (C-1), 66.8 (CH_2Ph), 128.2, 128.6, 136.7 (C-Ar), 156.6 (N*C*OOCH$_2$) ppm. HRMS (ES): m/z calcd. for $C_{13}H_{19}NO_3Na$

260.1263; found 260.1267. MS (EI): *m*/*z* (%) = 238 (7) [M + H]$^+$, 194 (36), 108 (67), 91 (100), 79 (19), 65 (14).

1-(Benzyloxycarbonyl)-1,2,3,4-tetrahydropyridine (17): Pyridinium chlorochromate (PCC; 273 mg, 1.27 mmol) and silica gel (273 mg) were dried for 24 h under vacuo and mixed and ground in a mortar. The resulting powder was suspended in anhydrous CH_2Cl_2 (20 mL). 5-(benzyloxycarbonylamino)pentanol (199 mg, 0.84 mmol) in anhydrous CH_2Cl_2 (10 mL) was added in one portion, and the reaction mixture was sonicated for 1 h and concentrated in vacuo. Filtration on a column of Florisil using diethyl ether as eluent allowed the isolation of **17** (160.5 mg, 0.74 mmol, 88%) as a colorless oil, which was stored under nitrogen at –20 °C. IR (NaCl disc): $\tilde{\nu}_{max}$ = 3092, 3069, 3035, 2941, 1703, 1650, 1409, 1345, 1258, 1179, 1136, 1107, 1040 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (two rotamers) = 1.79 (m, 2 H, 5-H), 2.00 (m, 2 H, 4-H), 3.60 (m, 2 H, 6-H), 4.83 (m, 0.5 H, 3-H), 4.94 (m, 0.5 H, 3-H), 5.16 (s, 2 H, CH_2Ph), 6.78 (d, J = 8.4 Hz, 0.5 H, 2-H), 6.88 (d, J = 8.4 Hz, 0.5 H, 2-H), 7.34–7.40 (m, 5 H, Ar-H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ (two rotamers) = 21.3, 21.5, 21.7 (C-4, C-5), 42.2, 42.4 (C-6), 67.4, 67.5 (CH_2Ph), 106.4, 106.8 (C-3), 124.9, 125.4 (C-2), 128.0, 128.1, 128.5, 136.4 (C-Ar), 153.2, 153.6 (N*C*OOCH$_2$) ppm. EIMS: *m*/*z* (%) = 218 (93) [M + H]$^+$, 174 (100), 128 (16), 107 (7), 91 (67), 82 (30), 65 (70).

***trans*-1-(Benzyloxycarbonyl)-3-iodo-2-methoxypiperidine (18):** A solution of *N*-iodosuccinimide (707 mg, 3.14 mmol) in anhydrous methanol (6 mL) was added under nitrogen to a solution of enamine **17** (568.8 mg, 2.62 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0 °C. Ice-bath cooling was maintained for 1 h, then the mixture was warmed progressively to room temp. After 16 h, the mixture was poured into a saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried (WA filter) and the solvent removed in vacuo to yield a solid residue that was purified by flash chromatography on silica gel (hexane/AcOEt, 9:1) affording **18** (855.1 mg, 2.28 mmol, 87%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (two rotamers) = 1.48 (m, 1 H, 5-H$_{ax}$), 1.82 (m, 1 H, 5-H$_{eq}$), 1.97 (m, 1 H, 4-H$_{ax}$), 2.08 (m, 1 H, 4-H$_{eq}$), 2.96 (m, 1 H, 6-H$_{ax}$), 3.17 (s, 1.8 H, OC*H*$_3$), 3.26 (s, 1.2 H, OC*H*$_3$), 4.00 (m, 1 H, 6-H$_{eq}$), 4.42 (s, 0.6 H, 3-H), 4.47 (s, 0.4 H, 3-H), 5.18 (s, 2 H, CH_2Ph), 5.48 (s, 0.5 H, 2-H), 5.60 (s, 0.5 H, 2-H), 7.26–7.38 (m, 5 H, H-Ar) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ (two rotamers) = 28.1 (C-4, C-5), 29.3, 29.6 (C-3), 38.2, 38.6 (C-6), 54.9 (OCH$_3$), 67.5 (CH_2Ph), 86.0, 86.3 (C-2), 128.0, 128.1, 136.5 (C-Ar), 155.7, 155.9 (N*C*OOCH$_2$) ppm. HRMS (ES): *m*/*z* calcd. for $C_{14}H_{18}INaNO_3$ 398.0229; found 398.0222). MS (EI): *m*/*z* (%) = 240 (9) [M$^{+\cdot}$ – CO_2 – CH_2Ph], 217 (31) [M$^+$ – I – OCH$_3$], 199 (100), 173 (87), 128 (34) [HI], 119 (22), 110 (39).

Diethyl *trans*-2-[(Benzyloxycarbonyl)-3-iodo-2-piperidinyl]malonate (19): Diethyl malonate (293 μL, 1.93 mmol) was added to a solution of $TiCl_4$ (212 μL, 1.93 mmol) in CH_2Cl_2 (1 mL) under nitrogen at 0 °C. After 5 min, diisopropylethylamine (1.93 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h and cooled to –6 °C before dropwise addition of a solution of **18** (603.3 mg, 1.61 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at –6 °C for 1 h and then quenched with a saturated aqueous solution of NH_4Cl (2 mL). The aqueous phase was extracted with CH_2Cl_2, the combined organic phases were dried, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate, 8:2) to afford **19** (756.5 mg, 2.02 mmol, 93% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (two rotamers) = 1.08 (m, 3 H, 4′-H$_3$), 1.27 (td, J = 0.9, 3.3 Hz, 3 H, 4′-H$_3$), 1.52 (m, 1 H, 4-H$_{ax}$), 1.82 (m, 1 H, 4-H$_{eq}$), 1.97 (m, 1 H, 3-H$_{eq}$), 2.05 (m, 1 H, 3-H$_{ax}$), 2.90 (td, J = 1.5, 6.6 Hz, 0.6 H, 5-H$_{ax}$), 2.99 (td, J = 1.2, 6.9 Hz, 0.4 H, 5-H$_{ax}$), 3.90 (m, 2 H, 1-H and 5-H$_{eq}$), 4.01 (m, 1 H, 2-H), 4.22 (m, 4 H, 3′-H$_4$), 4.66 (s, 0.5 H, 1′-H), 4.68 (s, 0.5 H, 1′-H), 5.06–5.32 (m, 2 H, CH_2Ph), 7.26–7.43 (m, 5 H, Ar-H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ (two rotamers) = 13.7, 13.8, 21.1, 21.5, 27.5, 28.0, 29.2, 29.3, 39.3, 39.7, 52.0, 52.1, 57.7, 58.3, 62.0, 62.1, 67.4, 67.6, 127.9, 128.3, 128.4, 136.5, 155.5, 165.7, 167.0 ppm. HRMS (ES): *m*/*z* calcd. for $C_{20}H_{26}INaNO_6$ 526.0703; found 526.0701.

Synthesis of 6 from 19: Trimethylsilyl iodide (64 μL, 0.45 mmol) was slowly added to a solution of piperidine **19** (114.1 mg, 0.23 mmol) in anhydrous acetonitrile (4 mL) and stirred under nitrogen at 0 °C. Ice-bath cooling was maintained for 1 h, then the mixture was warmed progressively to room temp. overnight and the mixture was concentrated under reduced pressure. Aqueous HCl (10%, 2 mL) was added to the residue with ice-cooling and the mixture was washed with diethyl ether. Ground α-tripiperideine (22.6 mg, corresponding to 0.27 mmol of Δ^1-piperideine) was added to the aqueous solution and the pH was raised to 2.5 by slow addition of KOH (2 M). After 16 h at room temp. under nitrogen the mixture was cooled in an ice bath, basified to pH 9 by addition of KOH and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried and the solvents evaporated to dryness. The resulting yellow oil was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH 10%, 98:2:0.1) to give **6** (49.0 mg, 0.15 mmol, 67%) as a colorless oil. The spectral properties of the isolated compound were identical to those recorded for the compound obtained previously starting from L-lysine.

***trans*-2-Allyl-1-(benzyloxycarbonyl)-3-iodopiperidine (21):** $BF_3{\cdot}OEt_2$ (44 μL, 0.35 mmol) was added to a stirred solution of **18** (65.5 mg, 0.18 mmol) and allyltrimethylsilane (56 μL, 0.35 mmol) in CH_2Cl_2 (1 mL) at –78 °C under nitrogen. After 2 h at –78 °C, a saturated aqueous solution of Na_2CO_3 was added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried (WA filter paper) and the solvents evaporated under vacuum to dryness. Flash chromatography of the residue on silica gel (hexane/EtOAc, 8:2) gave **21** (35.3 mg, 0.092 mmol, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (two rotamers) = 1.48 (m, 2 H, 5-H$_2$), 1.98 (m, 2 H, 4-H$_2$), 2.32 (m, 2 H, 1′-H$_2$), 2.80 (br. t, J = 12 Hz, 1 H, 6-H$_{ax}$), 4.08 (m, 1 H, 6-H$_{eq}$), 4.45–4.60 (m, 2 H, 3-H, 2-H), 4.93–5.05 (m, 2 H, 3′-H$_2$), 5.09 (s, 2 H, CH_2Ph), 5.60 (m, 1 H, 2′-H), 7.23–7.40 (m, 5 H, Ar-H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ (two rotamers) = 21.6, 28.9 (C-4, C-5), 31.5 (C-3), 35.0 (C-1′), 38.6 (C-6), 59.2 (C-2), 67.2 (CH_2Ph), 118.0 (C-3′), 127.8, 127.9, 128.4, 136.8 (C-Ar), 155.8 (N*C*OOCH$_2$) ppm. HRMS (ES): *m*/*z* calcd. for $C_{16}H_{21}INO_2$ 386.0617; found 386.0624.

***trans*-1-(Benzyloxycarbonyl)-3-bromo-2-methoxypiperidine (23):** Compound **23** was prepared (yield: 86%) according to the same procedure as utilized for preparing **18** from **17**, but by using NBS (1.2 equiv.) instead of NIS. Crude **23** was purified by flash chromatography on silica gel (hexane/EtOAc, 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ (two rotamers) = 1.44 (m, 1 H, 5-H$_{ax}$), 1.89 (m, 1 H, 5-H$_{eq}$), 1.95–2.33 (m, 2 H, 4-H$_2$), 2.98 (m, 1 H, 6-H$_{ax}$), 3.21 (s, 1.8 H, 1′-H), 3.29 (s, 1.2 H, 1′-H), 4.04 (m, 1 H, 6-H$_{eq}$), 4.29 (br. s, 1 H, 3-H), 5.19 (s, 2 H, CH_2Ph), 5.44 (s, 0.6 H, 2-H), 5.54 (s, 0.4 H, 2-H), 7.36 (m, 5 H, Ar-H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ (two rotamers) = 26.9 (C-4, C-5), 38.0, 38.4 (C-6), 49.3 (C-3), 54.9, 54.9 (C-1′), 67.4 (CH_2Ph), 85.1, 85.1 (C-2), 127.8, 128.1, 128.5, 136.4 (Ar-C), 155.7, 155.9 (N*C*OOCH$_2$) ppm. HRMS (ES): *m*/*z* calcd. for $C_{14}H_{18}BrNaNO_3$ 350.0368; found 350.0371.

***trans*-3-Bromo-2-methoxy-1-(methoxycarbonyl)piperidine (25):** Compound **25** was prepared (yield: 81%) according to the same procedure as utilized for preparing **18** from **16**, but by using NBS (1.2 equiv.) instead of NIS and methyl chloroformate instead of benzyl chloroformate. Crude **25** was purified by flash chromatography on silica gel (hexane/EtOAc, 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ (two rotamers) = 1.66 (m, 1 H, 5-H_{ax}), 1.90 (m, 1 H, 5-H_{eq}), 1.97–2.09 (m, 2 H, 4-H_{ax}, 4-H_{eq}), 2.97 (m, 1 H, 6-H_{ax}), 3.28 (s, 2 H, 1′-H_3), 3.34 (s, 1 H, 1′-H_3), 3.74 (s, 1 H, CO_2CH_3), 3.76 (s, 2 H, CO_2CH_3), 4.00 (m, 1 H, 6-H_{eq}), 4.31 (br. s, 1 H, 3-H), 5.34 (m, 0.5 H, 2-H), 5.50 (m, 0.5 H, 2-H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ (two rotamers) = 26.9 (C-4, C-5), 37.0, 37.4, 38.0, 38.3 (C-6), 49.1 (C-3), 52.9 (NHCOO*C*H$_3$), 54.9, 55.3, 55.7 (C-1′), 84.4, 84.7, 85.2 (C-2), 153.6, 154.0 (NH*C*OOCH$_3$) ppm. HRMS (ES): *m*/*z* calcd. for $C_8H_{14}BrNaNO_3$ 274.0055; found 274.0058.

[1-(Benzyloxycarbonyl)-3-bromopiperidinyl]acetone (24): A solution of **23** (564 mg, 1.61 mmol) in CH_2Cl_2 (0.8 mL) was added to a solution of $TiCl_4$ (177 μL, 1.61 mmol) in CH_2Cl_2 (1 mL) under nitrogen at –78 °C, followed directly by addition of isopropenylacetate (266 μL, 2.42 mmol). The reaction mixture was stirred at –78 °C for 1 h and then warmed progressively to room temp. After one night, the reaction mixture was poured into a mixture of cold brine and CH_2Cl_2 and stirred for 10 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc, 6:4) to afford **24** (108 mg, 0.29 mmol, 18% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (m, 1 H, 4-H_{ax}), 1.62 (m, 1 H, 4-H_{eq}), 2.03 (m, 2 H, 3-H_{ax}, 3-H_{eq}), 2.14 (s, 3 H, 3′-H_3), 2.74 (d, J = 7.4 Hz, 2 H, 1′-H_2), 2.88 (m, 1 H, 5-H_{ax}), 4.16 (m, 1 H, 5-H_{eq}), 4.41 (br. s, 1 H, 2-H), 5.02 (m, 1 H, 1-H), 5.15 (s, 2 H, CH_2Ph), 7.35 (m, 5 H, Ar-H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ = 26.4, 27.8, 30.1, 36.2, 39.4, 50.0, 54.6, 67.5, 127.9, 128.1, 128.6, 136.6, 155.9, 207.0 ppm. HRMS (ES): *m*/*z* calcd. for $C_{16}H_{20}BrNaNO_3$ 376.0524; found 376.0519.

[3-Bromo-1-(methoxycarbonyl)piperidinyl]acetone (26): Compound **26** was prepared (77% from **25**) according to the same procedure utilized for the preparation of **24** from **23**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (m, 1 H, 4-H_{ax}), 1.62 (m, 1 H, 4-H_{eq}), 2.02 (m, 2 H, 3-H_{ax}, 3-H_{eq}), 2.14 (s, 3 H, 3′-H_3), 2.68 (dd, J = 7.0, 15.0 Hz, 1 H, 1′-H), 2.73 (dd, J = 7.0, 15.0 Hz, 1 H, 1′-H), 2.79 (m, 1 H, 5-H_{ax}), 3.65 (s, 3 H, CO_2CH_3), 4.06 (m, 1 H, 5-H_{eq}), 4.33 (br. s, 1 H, 2-H), 4.90 (m, 1 H, 1-H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ = 27.0, 29.8, 30.8, 38.1, 40.5, 49.7, 52.7, 53.1, 155.6, 207.0 ppm. HRMS (ES): *m*/*z* calcd. for $C_{10}H_{16}BrNaNO_3$ 300.0211; found 300.0210.

Synthesis of 28: Trimethylsilyl iodide (167 μL, 1.16 mmol) was slowly added to a solution of **26** (108.0 mg, 0.39 mmol) in anhydrous acetonitrile (7 mL) at room temp. under nitrogen. After one night, the mixture was concentrated under reduced pressure and aqueous HCl (10%, 10 mL) was added to the residue. The resulting solution was washed with diethyl ether, then ground α-tripiperidein (38.8 mg, 0.47 mmol of Δ^1-piperidein) was added to the acid aqueous solution. The pH was raised to 2.5 by slow addition of KOH (2 M) and the mixture was stirred at this pH overnight at room temp. under nitrogen. The mixture was basified to pH 9 by addition of KOH (2 M) with ice cooling and then extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were combined, dried (WA filter paper), concentrated in vacuo to dryness, and the residual yellow oil was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH 10%, 97:3:0.1) to give **28** (52.8 mg, 0.24 mmol, 61%) as a colorless oil. IR (NaCl disc): $\tilde{\nu}_{max}$ = 2933, 2858, 2789, 2727, 1713, 1653, 1447, 1378, 1240, 1131, 1102 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.26 (m, 1 H, 8-H_α), 1.34 (qd, J = 2.4, 4.2 Hz, 1 H, 9-H_α), 1.47 (qt, J = 2.1, 6.3 Hz, 1 H, 7-H_α), 1.60 (m, 1 H, 7-H_β), 1.65 (m, 1 H, 3-H_α), 1.76 (m, 1 H, 2-H_α), 1.77–1.85 (m, 4 H, 2-H_β, 3-H_β, 8-H_β, 9-H_β), 1.96 (td, J = 1.2, 6.0 Hz, 1 H, 6-H_α), 2.19 (s, 3 H, 3′-H_3), 2.50 (m, 2 H, 4-H_α, 9a-H_α), 2.57 (m, 1 H, 1′-H), 2.64 (m, 1 H, 1-H_α), 2.82 (dd, J = 2.4, 8.4 Hz, 1 H, 1′-H), 2.84 (m, 1 H, 1-H_β), 2.90 (br. d, J = 5.4 Hz, 1 H, 6-H_β), 3.24 (qd, J = 1.2, 2.4 Hz, 1 H, 3a-H_α) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ = 23.0 (C-8), 25.0 (C-7), 25.3 (C-2), 30.1 (C-3), 31.1 (C-3′), 31.8 (C-9), 46.2 (C-1′), 50.0 (C-6), 51.2 (C-1), 65.3 (C-4), 69.1 (C-3a), 86.4 (C-9a), 207.7 (C-2′) ppm. HRMS (ES): *m*/*z* calcd. for $C_{13}H_{23}N_2O$ 223.1810; found 223.1804.

2-(Trimethylsilyloxy)-1-dodecene: Diisopropylamine (1.38 mL, 9.79 mmol) and *n*BuLi (1.38 M in hexane, 7.11 mL, 9.79 mmol) were added successively under vigorous stirring to freshly distilled THF (4 mL) under nitrogen at –78 °C. After 2 min, triethylamine (1.25 mL, 8.89 mmol), chlorotrimethylsilane (2.26 mL, 17.79 mmol), and 2-dodecanone (2 mL, 8.9 mmol) were added successively. After 15 min at –78 °C, the temperature was progressively allowed to rise to room temp. After one night, water was added and the mixture was extracted three times with pentane. The pentane extract was dried (WA filter paper) and the solvents evaporated under vacuum to dryness to give 2-(trimethylsilyloxy)-1-dodecene (1.868 g, 7.29 mmol, 82%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.25 [s, 9 H, $Si(CH_3)_3$], 0.94 (t, J = 6.3 Hz, 3 H, 12-CH_3), 1.33 (br. s, 14 H), 1.50 (m, 2 H, 4-H), 2.05 (t, J = 7.7 Hz, 2 H, 3-H), 4.08 (s, 2 H, 1-H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ = 2.8 [$Si(CH_3)_3$], 14.3 (C-12), 22.9, 27.0, 29.3, 29.6, 29.7, 29.8, 29.9, 32.1, 36.7 (C-3), 89.9 (C-1), 159.8 (C-2) ppm.

3-Bromo-2-(2-oxododecanyl)-1-(methoxycarbonyl)piperidine (27): A solution of **25** (33.2 mg, 0.13 mmol) in CH_2Cl_2 (0.1 mL) was added to a solution of $TiCl_4$ (14.5 μL, 0.13 mmol) in CH_2Cl_2 (0.3 mL) under nitrogen at –78 °C. Immediately thereafter, a solution of 2-(trimethylsilyloxy)-1-dodecene (57.3 mg, 0.22 mmol) in CH_2Cl_2 (0.1 mL) was added. The reaction mixture was stirred at –78 °C for 1 h and then warmed progressively to room temp. After one night, a brine solution was added and the resulting mixture was extracted three times with CH_2Cl_2. The organic extracts were gathered, dried (WA filter paper) and the solvents evaporated in vacuo to dryness. Flash chromatography of the residue on silica gel (hexane/EtOAc, 7:3) gave **27** (31.9 mg, 0.079 mmol, 60%) as a colorless oil. IR (NaCl disc): $\tilde{\nu}_{max}$ = 2926, 2853, 1702, 1444, 1410, 1368, 1264, 1204, 1187, 1114 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.4 Hz, 3 H, 12′-H), 1.26 (br. s, 16 H), 1.54 (m, 2 H, 5-H_{ax}, 5-H_{eq}), 2.02 (m, 2 H, 4-H_{ax}, 4-H_{eq}), 2.44 (t, J = 6.9 Hz, 2 H, 3′-H), 2.71 (dd, J = 3.0, 8.0 Hz, 2 H, 1′-H), 2.86 (m, 1 H, 6-H_{ax}), 3.71 (s, 3 H, OCH_3), 4.15 (m, 1 H, 6-H_{eq}), 4.40 (br. s, 1 H, 3-H), 4.94 (m, 1 H, 2-H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ = 14.1 (C-12′), 22.66, 22.69, 23.6, 27.7, 29.1, 29.3, 29.3, 29.4, 29.4, 29.4, 29.5, 29.5, 29.5, 29.5, 29.6, 31.9, 31.9, 31.9, 39.1 (C-3′), 43.0 (C-1′), 43.5 (C-6), 50.7 (C-3), 52.9 (NHCOO*C*H$_3$), 54.5 (C-2), 156.3 (NH*C*OOCH$_3$), 207.8 (C-2′) ppm. HRMS (ES): *m*/*z* calcd. for $C_{19}H_{34}BrNaNO_3$ 426.1620; found 426.1628

Formation of 29 from 27: Trimethylsilyl iodide (113 μL, 0.80 mmol) was added to a solution of **27** (106.9 mg, 0.26 mmol) in anhydrous chloroform under nitrogen at 0 °C. The mixture was heated at reflux for 24 h, and the solution was then evaporated to dryness under vacuum, and aqueous HCl (10%, 7 mL) was added. The aqueous acid solution was extracted with diethyl ether and the organic layer was evaporated in vacuo to dryness. Aqueous HCl (10%,

4 mL) and α-tripiperidein (25.9 mg, 0.32 mmol of Δ^1-piperidein) were added successively to the residue. The pH was increased to 2.7, and maintained constant at this value by dropwise addition of aqueous KOH (2 M). After one night of stirring at room temp. the mixture was brought to pH 9 and extracted three times with CH_2Cl_2. The organic layers were combined, dried (WA filter paper) and the solvents evaporated to dryness in vacuo. Flash chromatography of the residue on silica gel (CH_2Cl_2/MeOH/NH_4OH 10%, 95:5:0.1) gave **29** (48.5 mg, 0.14 mmol, 54%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.2 Hz, 3 H, 12′-H_3), 1.26 (br. s, 15 H, 8-H_α, 5′-H_2, 6′-H_2, 7′-H_2, 8′-H_2, 9′-H_2, 10′-H_2, 11′-H_2), 1.55 (m, 3 H, 7-H_α, 4′-H_2), 1.64 (br. d, J = 14 Hz, 1 H, 7-H_β), 1.70 (qd, J = 3.6, 10.2 Hz, 1 H, 9-H_α), 1.87 (m, 2 H, 3-H_α, 8-H_β), 1.98 (m, 5 H, 2-H_α, 2-H_β, 3-H_β, 6-H_α, 9-H_β), 2.44 (t, J = 7.2 Hz, 2 H, 3′-H_2), 2.62 (m, 1 H, 1′-H), 2.69 (m, 1 H, 4-H_α), 2.76 (dd, J = 3.0, 10.2 Hz, 1 H, 9a-H_α), 2.85 (m, 2 H, 1-H_α, 1′-H), 2.92 (br. d, J = 11 Hz, 1 H, 6-H_β), 3.23 (m, 1 H, 1-H_β), 3.62 (td, J = 4.8, 7.2 Hz, 1 H, 3a-H_α) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$): δ = 14.2 (C-12′), 22.7, 22.8, 23.7, 24.3, 25.2, 29.0, 29.2, 29.3, 29.4, 29.5, 29.6, 32.0 (C-3), 43.8 (C-3′), 31.8 (C-9), 44.7 (C-1′), 49.5 (C-6), 50.2 (C-1), 64.1 (C-4), 69.6 (C-3a), 85.0 (C-9a), 209.3 (C-2′) ppm. HRMS (ES): *m*/*z* calcd. for $C_{22}H_{41}N_2O$ 349.3219; found 349.3212.

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[1] J. C. Braekman, D. Daloze, J. M. Pasteels, P. Vanhecke, J. P. Declercq, V. Sinnwell, W. Francke, *Z. Naturforschung, Teil C* **1987**, *42*, 627–630.
[2] C. Devijver, P. Macours, J. C. Braekman, D. Daloze, J. M. Pasteels, *Tetrahedron* **1995**, *51*, 10913–10922.
[3] S. Leclercq, J. C. Braekman, D. Daloze, J. M. Pasteels, *Prog. Chem. Org. Nat. Prod.* **2000**, *79*, 115–229.
[4] W. R. Kem, K. Wildeboer, S. LeFrancois, M. Raja, W. Marszalec, J. C. Braekman, *Cell Mol. Neurobiol.* **2004**, *24*, 535–551.
[5] A. Rouchaud, J. C. Braekman, *Eur. J. Org. Chem.* **2009**, 2666–2674.
[6] M. Castillo, R. N. Gupta, Y. K. Ho, D. B. MacLean, I. D. Spenser, *Can. J. Chem.* **1970**, *48*, 2911–2918.
[7] G. Gopalakrishnan, J. L. Hogg, *J. Org. Chem.* **1985**, *50*, 1206–1212.
[8] B. Franck, D. Randau, *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 131.
[9] R. Sakai, K. Suzuki, K. Shimamoto, H. Kamiya, *J. Org. Chem.* **2004**, *69*, 1180–1185.
[10] D. R. Ijzendoorn, P. N. M. Botman, R. H. Blaauw, *Org. Lett.* **2006**, *8*, 239–242.
[11] H. Quast, R. Frank, A. Heublein, E. Schmitt, *Liebigs Ann. Chem.* **1979**, 83–101.
[12] N. De Kimpe, R. Verhé, L. De Buyck, N. Schamp, *Can. J. Chem.* **1984**, *62*, 1812–1816.
[13] D. R. Crist, N. J. Leonard, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 962–974.
[14] M. N. Matos, C. A. M. Afonso, R. A. Batey, *Tetrahedron* **2005**, *61*, 1221–1244.
[15] T. Shono, Y. Matsumura, K. Tsubata, *J. Am. Chem. Soc.* **1981**, *103*, 1172–1176.
[16] R. A. Pilli, C. D. F. Alves, M. A. Böckelmann, Y. P. Mascarenhas, J. G. Nery, I. Vencato, *Tetrahedron Lett.* **1999**, *40*, 2891–2894.
[17] T. Shono, Y. Matsumura, M. Ogaki, O. Onomura, *Chem. Lett.* **1987**, 1447–1450.
[18] H. O. House, L. J. Czuba, M. Gall, H. D. Olmstead, *J. Org. Chem.* **1969**, *34*, 2324–2336.
[19] T. Inokuchi, S. Takagishi, F. Akahoshi, S. Torii, *Chem. Lett.* **1987**, 1553–1556.
[20] S. Louwrier, M. Ostendorf, A. Boom, H. Hiemstra, W. N. Speckamp, *Tetrahedron* **1996**, *52*, 2603–2628.
[21] O. Okitsu, R. Suzuki, S. Kobayashi, *J. Org. Chem.* **2001**, *66*, 809–823.
[22] K. Yachi, K. Maeda, H. Shinokubo, K. Oshima, *Tetrahedron Lett.* **1997**, *38*, 5161–5164.
[23] G. P. Claxton, L. Allen, J. M. Grisard, *Org. Synth.* **1977**, *56*, 118–122.
[24] D. R. Bender, L. F. Bjeldanes, D. R. Knapp, H. Rapoport, *J. Org. Chem.* **1975**, *40*, 1264–1269.

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