Pyrrolidine and indolizidine alkaloids from chiral *N-tert*-butanesulfinyl imines derived from 4-halobutanal

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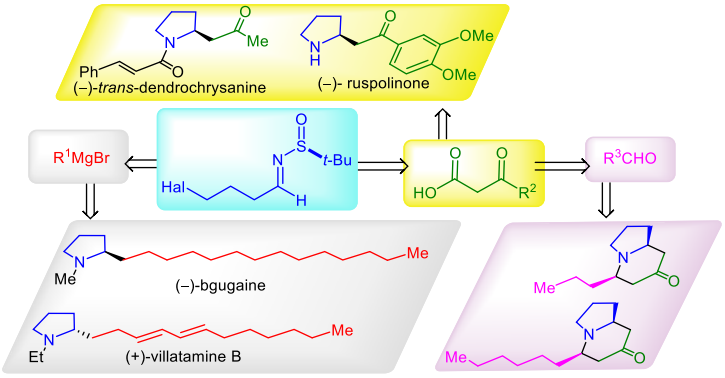
Dedicated to Professor Joaquín Plumet on the occasion of his 75th birthday



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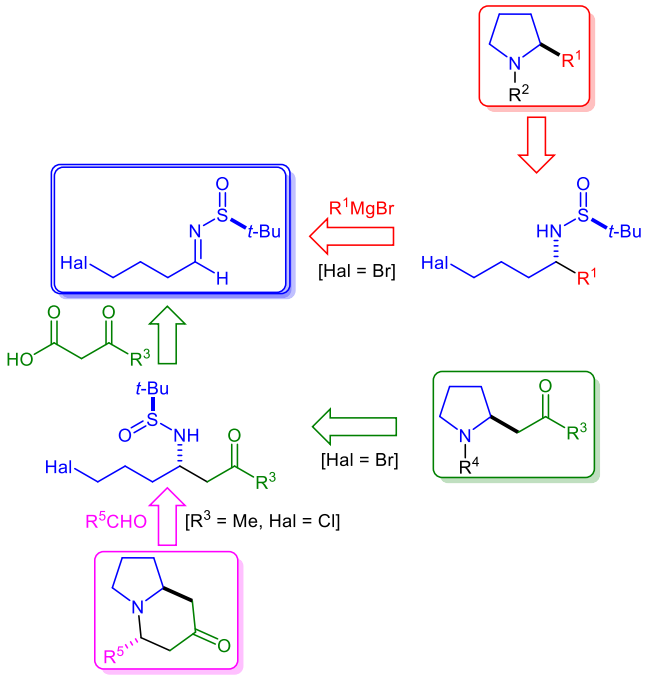
Abstract An efficient stereocontrolled preparation of 2-substituted pyrrolidines and 5-substituted indolizidin-7-ones, using chiral *N-tert*-butanesulfinyl imines derived from 4-halobutanal as starting materials, is detailed. Addition of Grignard reagents and decarboxylative Mannich reaction with β-keto acids involving these chiral imines proceeded with high diastereoselectivity. The synthesis of the pyrrolidinic alkaloids (–)-bgugaine, (+)-villatamine B, (–)-norhygrine, *trans*-dendrochrysanine and (–)-ruspolinone, demonstrated the utility of this methodology.

Key words chiral sulfinyl imines, diastereoselective additions, decarboxylative Mannich reaction, bgugaine, villatamine, norhygrine, *trans*-dendrochrysanine, ruspolinone

Not only the pyrrolidine ring is widely represented in nature, but also this molecular array is found in biologically active molecules, including approved commercial drugs. As a consequence, the number of synthetic methodologies which allows an expeditious access to these systems is constantly increasing. Most of these approaches consist in the formation of the five-membered ring through a cyclization process involving the nitrogen atom of an amine derivative, and a functional group located at an appropriate position along the hydrocarbon chain. Preparation of substituted pyrrolidines in a stereoselective fashion is of greater interest, and this can be achieved when the cyclization reactions are carried out using enantiopure precursors. Haloamines[1] and aminoalkenes[2] have been used as precursors in this type of transformations, the pyrrolidine ring being formed in the latter case through an intramolecular hydroamination reaction. Bicyclic systems containing bridgehead nitrogen, such as 1-azabicyclo[4.3.0]nonanes, the so called pirrolizidines, are also structural motifs less frequently encountered in alkaloids, with a six-membered ring fused to the pyrroline moiety, and these compounds could also display a wide range of biological activities.

On the other hand, chiral *N-tert*-butanesulfinyl imines have been extensively used as electrophiles in reactions with different nucleophilic species, among them, organometallic compounds. The electron withdrawing sulfinyl group bonded to the nitrogen atom facilitates the nucleophilic addition to the iminic carbon, and the configuration of the sulfur stereocenter plays an important role in controlling the stereochemical outcome of these transformations.[3] Since both enantiomers of the chiral aldimines are easily prepared from enantiopure commercially available *tert*-butanesulfinamide, along with the easily removal of the sulfinyl group under acidic conditions, and the development of practical procedures for recycling the chiral auxiliary, this strategy has became a potent tool to prepare chiral compounds with a nitrogen atom bonded to a stereogenic center, working even at large-scale. Continuing our interest in the use of *N-tert*-butanesulfinyl imines as electrophiles,[4] we envisioned a straightforward stereoselective synthesis of 2-substituted pyrrolidines and 5-substituted indolizidin-7-ones, based on the diastereoselective addition of Grignard reagents and β-keto acids to chiral imines derived from 4-halobutanal. The initially formed haloalkylamine derivatives will be transformed into the corresponding pyrrolidines upon intramolecular nucleophilic substitution involving the nitrogen atom, and the halogen atom as leaving group (Scheme 1). As far as we know, this strategy was also reported by Reddy and Prashad in the formation of 2-substituted pyrrolidines by diastereoselective addition of Grignard reagents to *N-tert*-butanesulfinyl imine of 4-chlorobutanal.[5] The same compounds can be accessed by performing a diastereoselective reduction of *N-tert*-butanesulfinyl γ-chlorobutyl ketimines.[6]

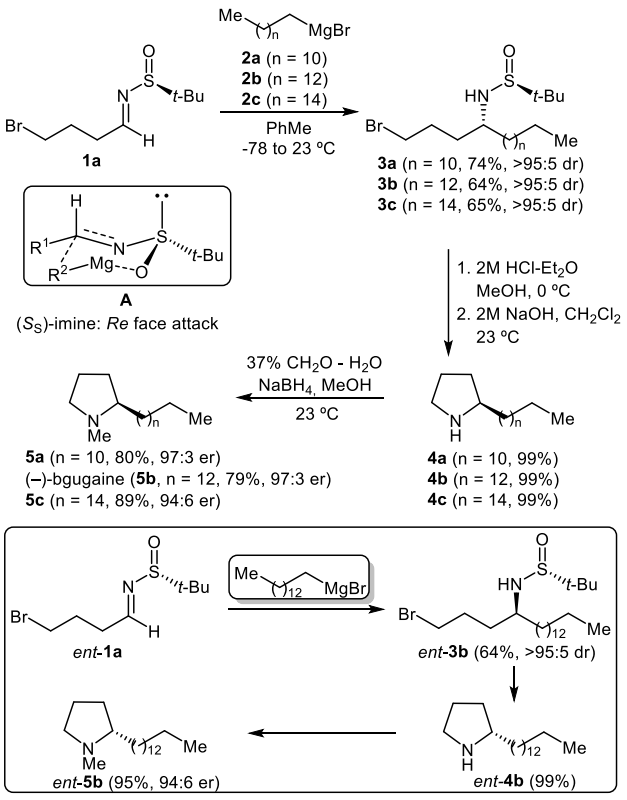
The addition of Grignard reagents to *N-tert*-butanesulfinyl aldimines proceeds with high levels of diastereocontrol when the reaction is performed in no coordinating solvents, such as dichloromethane and toluene.[7] The attack of the Grignard reagent occurred on the *Re* face of the imine with the *S* configuration at the sulfur atom, a cyclic six membered chelated transition state **A** being proposed to rationalize these experimental results (Scheme 2).[7b] This model was also consistent with the observed solvent effect. Taking into account



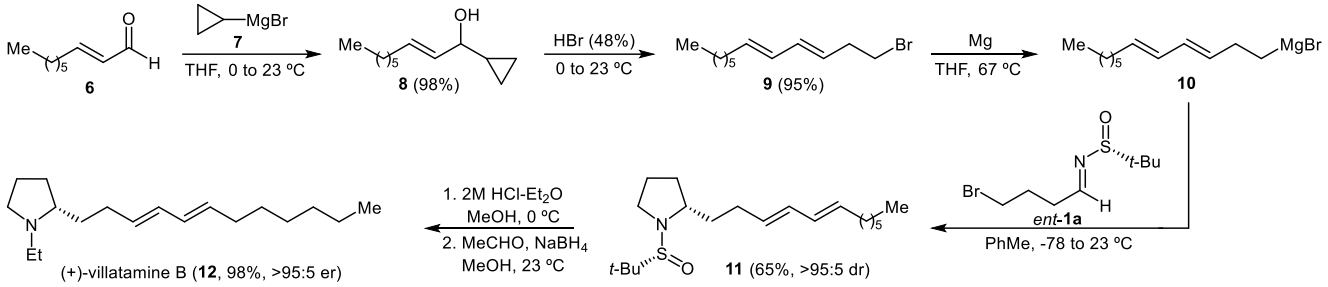
Scheme 1 Retrosynthetic analysis for the preparation of 2-substituted pyrrolidines and 5-substituted indolizidin-7-ones from *N-tert*-butanesulfinyl imines derived from 4-halobutanal

our experience in the diastereoselective addition of organomagnesium compounds to these imines,[8] we studied first the addition of a 1M solution of dodecylmagnesium bromide (**2a**) in ether to the imine **1a** derived from 4-bromobutanal and (*S*)-*tert*-butanesulfinamide in toluene. The addition was carried out at -78 °C, and after that, the reaction mixture was allowed to reach room temperature. The reaction product **3a** was obtained in 74% yield and excellent diastereoselectivity, and the configuration was assigned according to the mechanistic model **A** (Scheme 2). On the other hand, the reaction of chiral imine **1a** with tetradecyl- and hexadecylmagnesium bromide (**2b** and **2c**, respectively) provided compounds **3b** and **3c**, respectively, with similar yields and diastereoselectivities. Organomagnesium compounds **2** were prepared from the corresponding commercially available alkyl bromides upon reaction with magnesium in dry diethyl ether at 23 °C for 4 hours. The configuration of the newly created stereogenic center is determined by the configuration of the sulfur atom of the chiral aldimine. In this respect, the reaction of *ent*-**1a**, which derives from (*R*)-*tert*-butanesulfinamide, with tetradecylmagnesium bromide led to *ent*-**3b**, the enantiomer of **3b** (Scheme 2). Further removal of the sulfinyl group under acidic conditions in methanol as solvent, and subsequent treatment of the resulting ammonium salt under basic conditions gave the expected 2-substitued pyrrolidines **4** in quantitative yields. Final *N*-methylation of these heterocycles by treatment with excess of both aqueous formaldehyde and sodium borohydride, yielded *N*-methyl pyrrolidine derivatives **5**. Yields were excellent, and the enantiomeric ratios were also extremely high in this last transformation, and were determined using an *O*-aryl lactic acid derivative as a chiral solvating agent in ^{1}H NMR analysis.[9] It was not possible to determine the enantiomeric ratio in these compounds by means of HPLC or GC with chromatographic columns with a chiral packing. Compound **5b** is (−)-bgugaine,[10] an alkaloid isolated from the tubers of *Arisarum vulgare*, which is found on the Mediterranean coasts of Morocco and Spain.[11] This compound is a potent hepatotoxin in human liver cells, and has a strong binding affinity for DNA, displaying antibacterial and antimycotic activities.[12]

Taking advantage of the previously reported methodology, pyrrolidine alkaloid (+)-villatamine B (**12**) was synthesized from chiral bromoaldimine *ent*-**1a** and dodeca-3,5-dien-1-ylmagnesium bromide **10**. This Grignard reagent was prepared following the methodology developed by Davies and co-workers in the synthesis of (−)-pseudodistotimin E,[13] starting from (*E*)-non-2-enal (**6**). The addition of cyclopropylmagnesium bromide **7** to aldehyde **6** gave allylic alcohol **8** in high yield. Treatment of **8** with an aqueous solution of hydrogen bromide (48%) led to (3*E*,5*E*)-1-bromododeca-3,5-diene **9** as the major diastereoisomer, less than 10% of the (3*E*,5*Z*) and (3*Z*,5*E*) isomers being also formed. Organomagnesium compound **10** was prepared upon reaction of alkyl bromide **9** with magnesium, in the presence of a catalytic amount of iodine, in THF at 67 °C for 1 hour. The addition of this THF solution of compound **10** to a solution of chiral imine *ent*-**1a** in dry toluene at -78 °C, followed by stirring the reaction mixture to reach room temperature, produced, surprisingly, *N-tert*-butanesulfinyl pyrrolidine **11**. This compound was isolated as an almost single diastereoisomer after column chromatography purification, considering the configuration of the new stereocenter (only a singlet corresponding to the *t*-butyl group was observed in the ^{1}H NMR spectrum). Apparently, after nucleophilic addition of the Grignard reagent, the resulting magnesium amide underwent intramolecular cyclization, leading to **11**. The synthesis of (+)-villatamine B (**12**)[14] was finally accomplished



Scheme 2 Stereoselective synthesis of 2-substituted pyrrolidines from *N-tert*-butanesulfinyl bromoaldimines **1a**, including natural alkaloid (−)-bgugaine (**5b**)

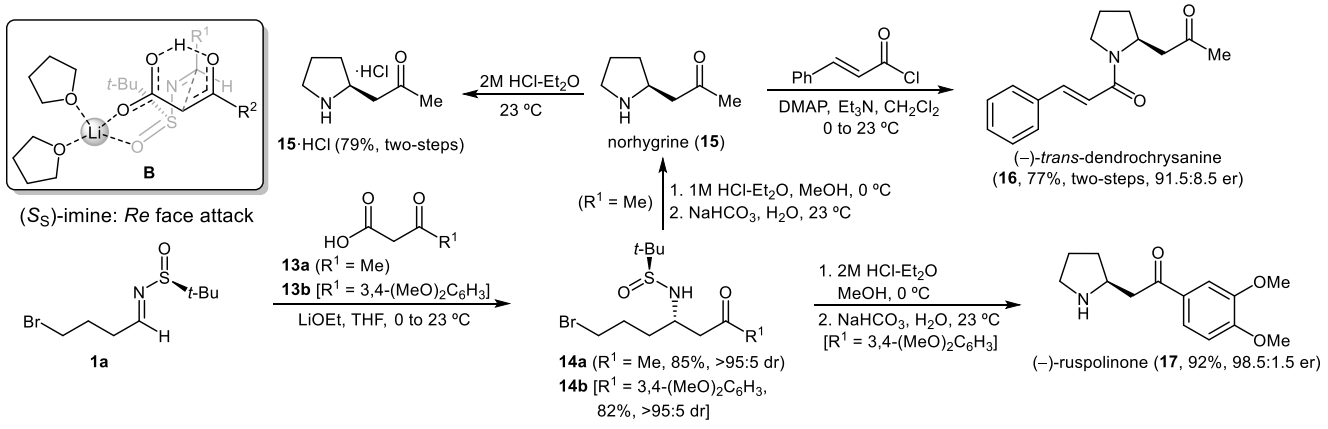


Scheme 3 Stereoselective synthesis of (+)-villatamine B (**12**) from *N*-*tert*-butanesulfinyl bromoaldimine *ent*-**1a**

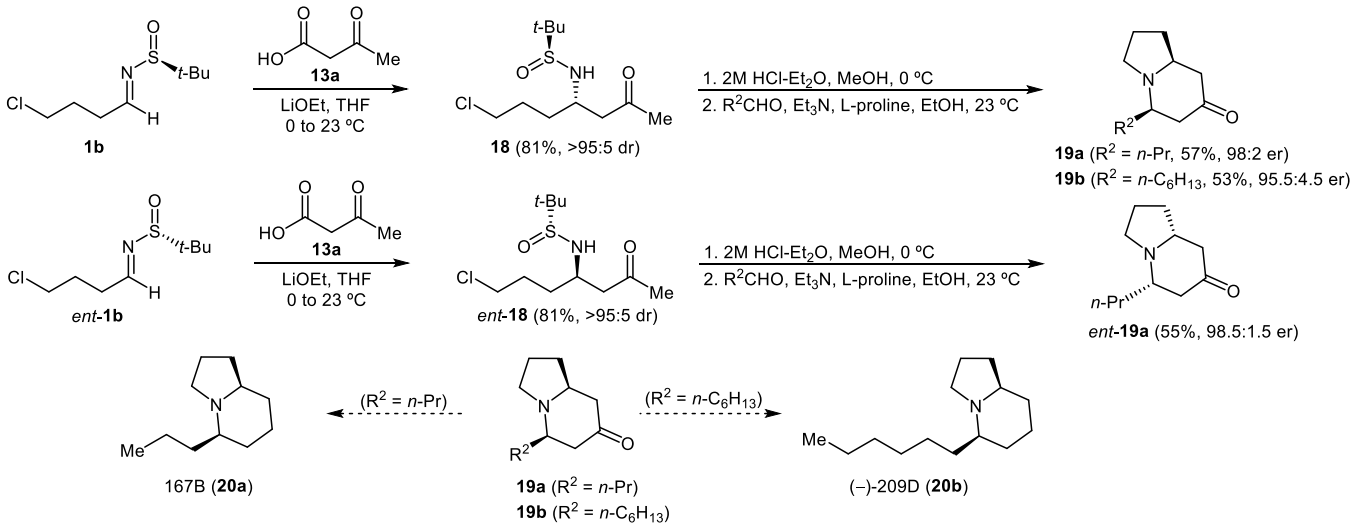
by carrying out desulfinylation under acidic conditions, and final *N*-ethylation through a reductive amination with propanal (Scheme 3). This marine alkaloid was isolated from the depredatory flatworm *Prostheceraeus vittatus* and its tunicate prey *Clavelina lepadiformis*, and exhibited cytotoxicity against different human cancer cell lines.[15]

We have found that the base-promoted decarboxylative-Mannich coupling of β-keto acids and *N*-*tert*-butanesulfinyl imines led to β-amino ketone derivatives in high yields and in a diastereoselective manner. In this case, the nucleophilic addition of the enolate took place to the *Re* face of imine with S_S configuration. Based on DFT calculations, an eight-membered cyclic transition state **B** was proposed to rationalize the experimental results (Scheme 4).[16] A straightforward synthesis of (–)-norhygrine (**15**) was accomplished by the diastereoselective coupling of 3-oxobutanoic acid (**13a**) and chiral imine **1a**. The base-promoted decarboxylative-Mannich coupling of these reagents led to β-amino ketone derivative **14a** in 85% isolated yield. Further removal of the sulfinyl group under acidic conditions, followed by intramolecular *N*-alkylation upon treatment with sodium bicarbonate, yielded (–)-norhygrine (**15**), that was easily isolated as its hydrochloride derivative (Scheme 4). Interestingly, *N*-acylation of (–)-norhygrine (**15**) with cinnamyl chloride led to (–)-*trans*-dendrochrysanine (**16**) in 77% yield, from β-amino ketone derivative **14a**. This alkaloid has been isolated from the stems of *Dendrobium chrysanthum*,[17] and according to ^{1}H and ^{13}C NMR spectra, compound **16** existed at room temperature as an interconverting 4:1 mixture of atropoisomers.[18] Decarboxylative coupling of β-keto acid **13b** and *N*-*tert*-butanesulfinyl imine **1a** led to β-amino ketone derivative **14b** in 82% yield, and it was transformed under the previously commented reaction conditions into (–)-ruspolinone (**17**) in 92% yield, an alkaloid isolated from *Ruspolia hypercrateriformis*, which has been proposed as biosynthetic precursor of septicine, tylophorine and related alkaloids (Scheme 4).[19]

It was also possible to carry out the stereoselective synthesis of the indolizidine skeleton from chiral *N*-*tert*-butanesulfinyl haloimines **1**. The base-promoted decarboxylative-Mannich coupling of 3-oxobutanoic acid (**13a**) and *N*-*tert*-butanesulfinyl imine **1b**, derived from 4-chlorobutanal, gave β-amino ketone derivative **18** in 81% yield. This compound participated in a L-proline organocatalyzed intramolecular Mannich reaction with an aldehyde (R^2CHO: *n*-butanal and *n*-heptanal) to give *cis*-2,6-disubstituted piperidin-4-ones,[20] first, followed by a subsequent intramolecular *N*-alkylation involving the carbon-chlorine bond, leading finally to the corresponding indolizidine **19**, in moderate yields (Scheme 5). Importantly, when the reaction was performed with bromine derivative **14a**, the expected indolizidines **19** were obtained in less than 10% yield, and a significant amount of (–)-norhygrine (**15**) was also formed. Apparently, when *N*-alkylation of the resulting free amine occurs first, after removal of the sulfinyl group, L-proline intramolecular Mannich reaction does not take place. Since alkyl bromides are better alkylating reagents than alkyl chlorides, thus the reason why, notably higher yields in the formation of indolizidines **19** were obtained starting from chloro derivative **18** instead of bromo derivative **14a**. Both enantiomers of 5-propylindolizidin-7-one (**19a** and *ent*-**19a**) are accessible



Scheme 4 Stereoselective synthesis of (–)-norhygrine (**15**), dendrochrysanine (**16**) and (–)-ruspolinone (**17**) from *N*-*tert*-butanesulfinyl bromoaldimine **1a**



Scheme 5 Stereoselective synthesis of indolizidinones **19a** and **19b** from *N*-*tert*-butanesulfinyl chloroaldimine **1b**

through this methodology, the configuration of the reaction product depending on the configuration of the sulfur atom of the starting chloroaldimine **1b** (S_S-configuration) and *ent*-**1b** (R_S-configuration). Enantiomeric ratios of compounds **19** were found to be excellent, and were determined by GC using a chromatographic column with a chiral packing (Scheme 5). Indolizidinones **19a** and **19b** could be considered direct precursors[21] of dendrobatid alkaloids 167D (**20a**) and (–)-209D (**20b**),[22] respectively.

In conclusion, we have developed methodologies for the enantioselective synthesis of 2-substituted pyrrolidines and 5-substituted indolizidin-7-ones, starting from *N*-*tert*-butanesulfinyl imines derived from 4-halobutanal. The stereochemical outcome of the nucleophilic addition of organomagnesium reagents and the decarboxylative Mannich reaction with 3-oxoalkanoic acids is governed by the configuration of the sulfur atom of the chiral sulfinyl unit. The formation of the pyrrolidine ring is achieved upon removal of the sulfinyl group under acidic conditions, followed by intramolecular *N*-alkylation. In addition, a L-proline organocatalyzed intramolecular Mannich reaction of β-amino ketone derivatives with an aldehyde led to the formation of 5-substituted indolizidin-7-ones. The usefulness of these methodologies was illustrated by the total synthesis of alkaloids such as (–)-bgugaine, (+)-villatamine B, (–)-norhygrine, *trans*-dendrochrysanine, (–)-ruspolinone, as well as by the synthesis of indolizidinones **19a** and **19b**, which can be considered direct precursors of dendrobatid indolizidine alkaloids 167D and (–)-209D.

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All reactions were performed in dry glassware using conventional Schlenck techniques under a static pressure of Ar, unless otherwise stated. Reagents and solvents were purchased from commercial suppliers and used as received. *tert*-Butanesulfinamides (*R* and *S*) were a gift from Medalchemy (>99% ee by chiral HPLC on a Chiracel AS column, 90:10 *n*-hexane/*i*-PrOH, 1.2 mL/min, λ=222 nm). TLC was performed on silica gel 60 F_{254}, using aluminum plates and visualized with phosphomolybdic acid (PMA) stain. Flash chromatography was carried out on handpacked columns of silica gel 60 (230- 400 mesh). Melting points are uncorrected. Optical rotations were measured using a Jasco P-1030 polarimeter with a thermally jacketed 5 cm cell at approximately 23 °C and concentrations (*c*) are given in g/100 mL. Enantiomeric ratios were determined by gas liquid chromatography (GLC) on an Agilent 6890N Network gas chromatograph equipped with a CP-Chirasil-Dex CB column. Infrared analyses were performed with an ATR Jasco FT/IR-4100 spectrophotometer; wave numbers are given in cm^{-1}. Low-resolution mass spectra (EI) were obtained with an Agilent GC/MS5973N spectrometer at 70 eV; and fragment ions in *m/z* with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were also carried out in the electron impact mode (EI) at 70 eV and on a Finnigan MAT95S spectrometer equipped with a time of flight (TOF) analyzer and the samples were ionized by ESI techniques and introduced through an ultra-high pressure liquid chromatography (UPLC) model. ^{1}H NMR spectra were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR with a Bruker AV300 Oxford or a Bruker AV400 spectrometer, respectively, using $CDCl_3$ and CD_3OD as solvents, and TMS as internal standard (0.00 ppm). The data are reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br s = broad signal, coupling constant(s) in Hz, integration. ^{13}C NMR spectra were recorded with ^{1}H-decoupling at 100 MHz and referenced to $CDCl_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, CH_2 and CH_3. Imines **1a**[23] and **1b**,[5] were prepared from the corresponding aldehyde and (*R*)- or (*S*)-*tert*-butanesulfinamide in THF, in the presence of two equivalents of titanium tetraethoxide. Compounds **13** were prepared by hydrolysis of the corresponding β-ketoester.

Diastereoselective Addition of Grignard Reagents 2 to Bromoaldimines 1; General Procedure

The corresponding alkyl bromide (5.00 mmol) was added dropwise to a suspension of Mg turnings (0.180 g, 7.50 mmol, 1.5 equiv) in dry Et_2O (3.00 mL). Then a catalytic amount of 1,2-dibromoethane (18.0 µL, 0.25 mmol, 5 mol%) was added and the solution was stirred at room temperature for 4 h. The resulting solution of alkylmagnesium bromide (**2**, ~1.1 M in Et_2O, 1.20 mL, 1.25 mmol, 2.5 equiv) was slowly added to a solution of aldimine **1a** (0.127 g, 0.50 mmol) in dry toluene (2.50 mL) at -78 °C. The reaction was allowed to reach room temperature over 15 h. After that, it was cooled down to 0 °C, hydrolyzed with water (10 mL) and extracted with EtOAc (3 × 15 mL). The organic layers were successively washed with water (15 mL), brine (10 mL) and then dried over magnesium sulfate, and concentrate under vacuum (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc: 5/1) to yield pure compounds **3**.

(4*R*,*S*$_S$)-*N*-(*tert*-Butanesulfinyl)-1-bromohexadecan-4-amine (3a)

Purification by flash column chromatography on silica gel using hexane/EtOAc (5:1) afforded **3a** as a colorless oil; yield: 0.156 g (74%); R_f = 0.45 (hexane/EtOAc 2:1).

$[\alpha]^{20}_D$: +7.0 (*c* 1.14, CH_2Cl_2)

IR (neat): 2923, 2854, 1461, 1365, 1253, 1052, 728 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.41 (t, *J* = 6.6 Hz, 2H), 3.27-3.19 (m, 1H), 2.98 (d, *J* = 6.6 Hz, 1H), 2.03-1.83 (m, 2H), 1.73-1.48 (m, 4H), 1.28-1,25 (m, 20H), 1.21 (s, 9H), 0.90-0.85 (m, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 56.1 (CH), 56.0 (C), 36.7 (CH_2), 34.2 (CH_2), 33.8 (CH_2), 32.1 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.75 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 28.9 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3).

MS (EI): *m*/z (%) = 425 (M^++2, 0.05%), 423 (M^+, 0.03%), 369 (31), 367 (32), 352 (13), 350 (12), 246 (14), 198 (25), 152 (14), 150 (14), 118 (16), 97 (12), 85 (20), 83 (18), 71 (30), 70 (60), 69 (19), 57 (100), 55 (20), 43 (34), 41 (27).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{16}H_{32}N$ [M^+-$C_4H_{10}BrOS$]: 238.2535; found: 238.2529.

(4*R*,*S*$_S$)-*N*-(*tert*-Butanesulfinyl)-1-bromooctadecan-4-amine (3b)

Purification by flash column chromatography on silica gel using hexane/EtOAc (5:1) afforded **3b** as a colorless oil; yield: 0.144 g (64%); R_f = 0.46 (hexane/EtOAc 2:1).

$[\alpha]^{20}_D$: +13.7 (*c* 0.94, CH_2Cl_2).

IR (neat): 2919, 2854, 1461, 1369, 1265, 1056, 736 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.41 (t, *J* = 6.6 Hz, 2H), 3.27-3.19 (m, 1H), 2.99 (d, *J* = 6.7 Hz, 1H), 2.04-1.81 (m, 2H), 1.77-1.49 (m, 4H), 1.29-1,25 (m, 24H), 1.22 (s, 9H), 0.92-0.84 (m, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 56.1 (CH), 56.0 (C), 36.7 (CH_2), 34.2 (CH_2), 33.8 (CH_2), 32.1 (CH_2), 29.9 (CH_2), 29.85 (CH_2), 29.8 (CH_2), 29.75 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 28.9 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3).

MS (EI): *m*/z (%) = 453 (M^++2, 0.02%), 451 (M^+, 0.01%), 397 (35), 395 (34), 380 (11), 378 (11), 315 (20), 274 (15), 200 (10), 198 (10), 118 (42), 97 (10), 85 (22), 83 (16), 71 (30), 70 (54), 69 (17), 57 (100), 55 (20), 43 (26), 41 (27).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{18}H_{38}{}^{79}BrNOS$ [M^+-C_4H_8]: 395.1857; found: 395.1687.

(4*S*,*R*$_S$)-*N*-(*tert*-Butanesulfinyl)-1-bromooctadecan-4-amine (*ent*-3b)

Starting from aldimine *ent*-**1a**, and after purification by flash column chromatography on silica gel using hexane/EtOAc (5:1) afforded *ent*-**3b** as a colorless oil; yield: 0.144 g (64%). Physical and spectroscopical data were found to be the same as for **3b**.

$[\alpha]^{20}_D$: −23.9 (*c* 1.04, CH_2Cl_2).

(4*R*,*S*$_S$)-*N*-(*tert*-Butanesulfinyl)-1-bromododecan-4-amine (3c)

Purification by flash column chromatography on silica gel using hexane/EtOAc (5:1) afforded **3c** as a colorless wax; yield: 0.155 g (65%); R_f = 0.50 (hexane/EtOAc 2:1).

$[\alpha]^{20}_D$: +18.7 (*c* 1.09, CH_2Cl_2).

IR (neat): 2923, 2854, 1461, 1369, 1253, 1052, 728 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.41 (t, *J* = 6.6 Hz, 2H), 3.29-3.19 (m, 1H), 2.99 (d, *J* = 6.6 Hz, 1H), 2.02-1.87 (m, 2H), 1.77-1.48 (m, 4H), 1.30-1,24 (m, 28H), 1.22 (s, 9H), 0.91-0.84 (m, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 56.1 (CH), 56.0 (C), 36.7 (CH_2), 34.2 (CH_2), 33.8 (CH_2), 32.1 (CH_2), 29.9 (CH_2), 29.85 (CH_2), 29.8 (CH_2), 29.75 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 28.9 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3).

MS (EI): *m*/z (%) = 481 (M^++2, 0.02%), 479 (M^+, 0.01%), 425 (34), 423 (33), 406 (10), 344 (11), 343 (37), 302 (13), 118 (64), 85 (21), 83 (17), 71 (31), 70 (100), 69 (19), 57 (92), 55 (22), 43 (31), 41 (26)

HRMS (ESI-TOF): *m*/*z* calcd for $C_{20}H_{40}N$ [M^+-$C_4H_{10}BrOS$]: 294.3161; found: 294.3161.

Synthesis of Pyrrolidines 4 from Bromoalkyl Sulfinamides 3; General Procedure

To a solution of the corresponding bromoalkyl sulfinamide **3** (0.15 mmol) in MeOH (1.50 mL) was added a 2M solution of HCl in Et_2O (0.75 mL, 1.50 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 30 min. Complete formation of the corresponding free amine hydrochloride was followed by TLC. After that, solvents were evaporated (15 Torr), and to the resulting residue was dissolved in CH_2Cl_2 (1.00 mL). A 2M aqueous solution of NaOH (1.00 mL) was slowly added at 0 °C, and the reaction mixture was stirred for 2 h at the same temperature. Then the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 x 5 mL). The combined organic layers were dried over magnesium sulfate, and concentrate under vacuum (15 Torr). The residue was the corresponding pure compound **4**.

(*R*)-2-Dodecylpyrrolidine (4a)

Compound **4a** was isolated as a yellow wax; yield: 0.036 g (99%); R_f = 0.61 (CH_2Cl_2/MeOH 10:1).

$[\alpha]^{20}_D$: −13.3 (*c* 0.88, MeOH).

IR (neat): 2923, 2854, 1457, 1033, 721 cm^{-1}.

^1H NMR (CD_3OD, 400 MHz): δ = 3.05-2.96 (m, 2H), 2.88-2.80 (m, 1H), 2.01-1.92 (m, 1H), 1.86-1.72 (m, 2H), 1.61-1.43 (m, 4H), 1.31-1,27 (m, 20H), 0.92-0.87 (m, 3H).

^{13}C NMR (CD_3OD, 100 MHz): δ = 60.8 (CH), 46.8 (CH_2), 36.1 (CH_2), 33.1 (CH_2), 32.5 (CH_2), 30.9 (CH_2), 30.8 (CH_2), 30.75 (CH_2), 30.7 (CH_2), 30.65 (CH_2), 30.5 (CH_2), 28.5 (CH_2), 25.7 (CH_2), 23.7 (CH_2), 14.4 (CH_3).

MS (EI): *m*/z (%) = 239 (M^+, 2.20%), 238 (7), 98 (2), 96 (4), 83 (4), 71 (12), 70 (100), 57 (4), 56 (6), 55 (7).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{16}H_{32}N$ [M^+-H]: 238.2535; found: 238.2529.

(*R*)-2-Tetradecylpyrrolidine (4b)

Compound **4b** was isolated as a white solid; mp 58-59 °C (hexane/CH_2Cl_2) (lit.[24] mp 56-58 °C); yield: 0.040 g (99%); R_f = 0.62 (CH_2Cl_2/MeOH 10:1).

$[\alpha]^{20}_D$: −9.1 (*c* 0.87, MeOH) [lit.[23] $[\alpha]^{20}_D$: −7.1 (*c* 1.10, MeOH)].

IR (neat): 2915, 2850, 1461, 910, 725 cm^{-1}.

^1H NMR (CD_3OD, 300 MHz): δ = 3.04-2.89 (m, 2H), 2.85-2.75 (m, 1H), 2.00-1.88 (m, 1H), 1.85-1.72 (m, 2H), 1.60-1.40 (m, 4H), 1.31-1,28 (m, 24H), 0.92-0.88 (m, 3H).

^{13}C NMR (CD_3OD, 75 MHz): δ = 60.7 (CH), 46.8 (CH_2), 36.5 (CH_2), 33.1 (CH_2), 32.6 (CH_2), 30.85 (CH_2), 30.8 (CH_2), 30.75 (CH_2), 30.7 (CH_2), 30.65 (CH_2), 30.5 (CH_2), 28.5 (CH_2), 25.9 (CH_2), 23.7 (CH_2), 14.4 (CH_3).

MS (EI): *m*/z (%) = 267 (M^+, 0.43%), 266 (1), 110 (1), 96 (3), 83 (7), 71 (5), 70 (100), 55 (3).

(*S*)-2-Tetradecylpyrrolidine (*ent*-4b)

Starting from bromoalkyl sulfinamide *ent*-**3b**, compound *ent*-**4b** was isolated as a white solid; yield: 40 mg (99%). Physical and spectroscopical data were found to be the same as for **4b**.

$[\alpha]^{20}_D$: +8.3 (*c* 0.50, MeOH).

(*R*)-2-Hexadecylpyrrolidine (4c)

Compound **4c** was isolated as a white solid; mp 40-41 °C (hexane/CH_2Cl_2); yield: 0.044 g (99%); R_f = 0.63 (CH_2Cl_2/MeOH 10:1).

$[\alpha]^{20}_D$: −1.15 (*c* 1.29, MeOH).

IR (neat): 2923, 2854, 1457, 1029, 721 cm^{-1}.

^1H NMR (CD_3OD, 500 MHz): δ = 3.05-2.97 (m, 2H), 2.89-2.82 (m, 1H), 2.01-1.94 (m, 1H), 1.87-1.74 (m, 2H), 1.62-1.38 (m, 4H), 1.32-1,27 (m, 28H), 0.90 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (CD_3OD, 125 MHz): δ = 60.9 (CH), 46.8 (CH_2), 36.1 (CH_2), 33.1 (CH_2), 32.4 (CH_2), 30.85 (CH_2), 30.8 (CH_2), 30.75 (CH_2), 30.7 (CH_2), 30.65

(CH_2), 30.6 (CH_2), 30.55 (CH_2), 30.4 (CH_2), 28.4 (CH_2), 25.7 (CH_2), 23.7 (CH_2), 14.4 (CH_3).

MS (EI): *m*/z (%) = 295 (M^+, 0.41%), 294 (1), 96 (1), 83 (2), 71 (5), 70 (100), 68 (2), 57 (3), 56 (2), 55 (3).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{20}H_{40}N$ [M^+-H]: 294.3161; found: 294.3159.

***N*-Methylation of Pyrrolidines 4; General Procedure**

To a solution of the corresponding pyrrolidine **4** (0.15 mmol) in MeOH (1.00 mL) was added aqueous HCHO (37%m 0.11 mL, 0.120 g, 1.50 mmol) and $NaBH_4$ (0.057 g, 1.50 mmol) at 23 °C. The reaction mixture was stirred at the same temperature for 4 h. After that, solvents were evaporated (15 Torr), and to the resulting residue was added CH_2Cl_2 (2.00 mL), and a 2M aqueous solution of NaOH (2.00 mL). The resulting mixture was stirred for 2 h. Then the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 x 5 mL). The combined organic layers were dried over magnesium sulfate, and concentrate under vacuum (15 Torr). The residue was the corresponding pure compound **5**.

(*R*)-2-Dodecyl-1-methylpyrrolidine (5a)

Compound **5a** was isolated as a yellow wax; yield: 0.030 g (80%); R_f = 0.68 (CH_2Cl_2/MeOH 10:1).

$[\alpha]^{20}_D$: −33.0 (*c* 0.67, MeOH).

IR (neat): 2923, 2854, 2776, 1457, 1168, 721 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.11-3.02 (m, 1H), 2.30 (s, 3H), 2.16-2.08 (m, 1H), 1.99-1.87 (m, 1H), 1.82-1.60 (m, 4H), 1.52-1.39 (m, 2H), 1.28-1,24 (m, 20H), 0.93-0.84 (m, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 66.7 (CH), 57.5 (CH_2), 40.6 (CH_3), 34.0 (CH_2), 32.1 (CH_2), 31.0 (CH_2), 30.2 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 26.9 (CH_2), 22.8 (CH_2), 22.0 (CH_2), 14.2 (CH_3).

MS (EI): *m*/z (%) = 253 (M^+, 2.52%), 252 (7), 110 (3), 97 (2), 96 (2), 84 (100), 82 (7), 69 (3), 68 (1), 57 (2), 56 (2), 55 (7).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{17}H_{34}N$ [M^+-H]: 252.2691; found: 252.2690.

(−)-Bgugaine [(*R*)-1-Methyl-2-tetradecylpyrrolidine (5b)]

Compound **5b** was isolated as a yellow oil; yield: 0.032 g (79%); R_f = 0.68 (CH_2Cl_2/MeOH 10:1).

$[\alpha]^{20}_D$: −39.9 (*c* 0.75, MeOH) [lit.[25] $[\alpha]^{20}_D$: −45.0 (*c* 1.20, MeOH)].

IR (neat): 2923, 2854, 1461, 1122, 725 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.10-3.04 (m, 1H), 2.31 (s, 3H), 2.16-2.10 (m, 1H), 2.01-1.87 (m, 1H), 1.81-1.61 (m, 4H), 1.47-1,42 (m, 2H), 1.29-1.25 (m, 24H), 0.88 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 60.7 (CH), 57.5 (CH_2), 40.6 (CH_2), 34.0 (CH_2), 32.1 (CH_2), 31.0 (CH_2), 30.2 (CH_2), 29.85 (CH_2), 29.80 (CH_2), 29.75 (CH_2), 29.5 (CH_2), 26.9 (CH_2), 22.8 (CH_2), 22.0 (CH_2), 14.2 (CH_3).

MS (EI): *m*/z (%) = 281 (M^+, 0.53%), 280 (1), 94 (1), 85 (6), 84 (100), 82 (2), 55 (2).

(+)-Bgugaine [(*S*)-1-Methyl-2-tetradecylpyrrolidine (*ent*-5b)]

Starting from bromoalkyl sulfinamide *ent*-**4b**, compound *ent*-**5b** was isolated as a yellow oil; yield: 0.040 g (95%). Physical and spectroscopical data were found to be the same as for **5b**.

$[\alpha]^{20}_D$: +32.9 (*c* 0.72, MeOH).

(*R*)-2-Hexadecyl-1-methylpyrrolidine (5c)

Compound **5c** was isolated as a white solid; mp 30-32 °C (hexane/CH_2Cl_2); yield: 42 mg (89%); R_f = 0.69 (CH_2Cl_2/MeOH 10:1).

$[\alpha]^{20}_D$: −39.1 (*c* 0.42, MeOH).

IR (neat): 2915, 2850, 1461, 1168, 725 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.11-3.01 (m, 1H), 2.30 (s, 3H), 2.18-2.06 (m, 1H), 1.98-1.92 (m, 1H), 1.87-1.55 (m, 4H), 1.51-1,33 (m, 2H), 1.29-1.25 (m, 28H), 0.92-0.84 (m, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 66.7 (CH), 57.5 (CH_2), 40.6 (CH_3), 34.0 (CH_2), 32.1 (CH_2), 31.0 (CH_2), 30.2 (CH_2), 29.85 (CH_2), 29.8 (CH_2), 29.75 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 26.9 (CH_2), 22.8 (CH_2), 22.0 (CH_2), 14.2 (CH_3).

MS (EI): *m*/z (%) = 309 (M^+, 3.35%), 308 (12), 110 (3), 97 (2), 96 (2), 85 (15), 84 (100), 82 (6), 70 (3), 69 (4), 56 (3), 55 (7).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{21}H_{42}N$ [M^+-H]: 308.3317; found: 308.3316.

(*E*)-1-Cyclopropylnon-2-en-1-ol (8)

Cyclopropyl bromide (1.452 g, 1.05 mL, 12.00 mmol) was added dropwise to a suspension of Mg turnings (0.432 g, 18.00 mmol, 1.5 equiv) in dry THF (7.20 mL). Then a catalytic amount of 1,2-dibromoethane (43.0 µL, 0.60 mmol, 5 mol%) was added, and the solution was stirred at room temperature for 4 h. The resulting solution of cyclopropylmagnesium bromide (**7**, ~1.1 M in THF, 5.50 mL, 6.00 mmol) was slowly added to a solution of (*E*)-non-2-enal (**6**, 0.420 g, 0.50 mL, 3.00 mmol) in dry THF (6.50 mL) at -0 °C. The reaction was allowed to reach room temperature over 15 h. After that, it was cooled down to 0 °C, hydrolyzed with a saturated aqueous solution of NH_4Cl (5.00 mL), and extracted with Et_2O (3 × 10 mL). The organic layers were dried over magnesium sulfate, and concentrate under vacuum (15 Torr). The residue was pure enough for the next step, affording **8** as a yellow oil; yield: 0.535 g (98%); R_f = 0.32 (hexane/Et_2O 3:1).

IR (neat): 3347, 3077, 2923, 2857, 1457, 1014, 968, 917 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.70-5.62 (m, 1H), 5.58-5.50 (m, 1H), 3.48-3.42 (m, 1H), 2.07-1.99 (m, 2H), 1.75 (br s, 1H), 1.40-1.34 (m, 2H), 1.33-1.21 (m, 6H), 1.04-0.93 (m, 1H), 0.91-0.84 (m, 3H), 0.57-0.45 (m, 2H), 0.36-0.29 (m, 1H), 0.25-0.18 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 132.3 (CH), 131.4 (CH), 77.2 (CH), 32.4 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 22.7 (CH_2), 17.7 (CH), 14.2 (CH_3), 3.1 (CH_2), 2.1 (CH).

MS (EI): *m*/z (%) = 182 (M^+, 6.45%), 164 (21), 154 (19), 110 (21), 98 (15), 97 (100), 93 (43), 91 (30), 84 (32), 83 (64), 81 (28), 80 (27), 79 (77), 77 (26), 70 (42), 69 (50), 67 (38), 57 (20), 55 (63).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{12}H_{22}O$ [M^+]: 182.1671; found: 182.1678.

(3*E*,5*E*)-1-Bromododeca-3,5-diene (9)

A concentrated aqueous solution of HBr (48%, 0.50 mL, 4.40 mmol, 4.0 equiv) was added to a 10 mL flask containing (*E*)-1-cyclopropylnon-2-en-1-ol (**8**, 0.200 g, 1.10 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 15 h. After that, hexane (15.0 mL) and H_2O (10.0 mL) were successively added. Then the layers were separated, and the aqueous layer was extracted with hexane (3 x 15 mL). The combined organics were dried over magnesium sulfate, and concentrate under vacuum (15 Torr). The residue was purified by flash column chromatography on silica gel using petroleum ether, affording **9** [90:5:5 mixture of (*E*,*E*):(*E*,*Z*):(*Z*:*E*) isomers] as a colorless oil; yield: 0.256 g (95%); R_f = 0.73 (hexane).

IR (neat): 3012, 2923, 2857, 1454, 987, 732 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 6.14-5.95 (m, 2H), 5.65 (dt, *J* = 14.3, 7.0 Hz, 1H), 5.52 (dt, *J* = 14.6, 7.0 Hz, 1H), 3.38 (t, *J* = 7.1 Hz, 2H), 2.62 (q, *J* = 7.1 Hz, 2H), 2.06 (q, *J* = 7.9 Hz, 2H), 1.42-1.34 (m, 2H), 1.33-1.23 (m, 6H), 0.91-0.87 (m, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 134.8 (CH), 133.4 (CH), 129.8 (CH), 127.6 (CH), 36.1 (CH_2), 32.8 (CH_2), 32.5 (CH_2), 31.9 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 22.7 (CH_2), 14.2 (CH_3).

MS (EI): *m*/z (%) = 246 (M^++2, 21.17%), 244 (M^+, 21.03%), 162 (29), 160 (29), 95 (27), 93 (30), 91 (26), 81 (100), 80 (19), 79 (50), 77 (32), 67 (57), 55 (16).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{12}H_{21}{}^{79}Br$ [M^+]: 244.0827; found: 244.0818.

(2*S*,*R*$_S$)-1-(*tert*-Butanesulfinyl)-2-[(3*E*,5*E*)-dodeca-3,5-dien-1-yl]pyrrolidines (11)

A small portion (0.25 mL) of a solution of the (3*E*,5*E*)-1-bromododeca-3,5-diene (**9**, 0.610 g, 2.50 mmol) in dry THF (2.50 mL) was added dropwise to Mg turnings (0.096 g, 3.75 mmol, 1.5 equiv) and I_2 (0.006 g, 0.0025 mmol, 10 mol%) at room temperature. This suspension was then heated with a heat gun until the solvent started to reflux. The rest of the solution of the (*E*,*E*)-1-bromododeca-3,5-diene (**9**) in THF was added to the reaction flask, and the mixture was heated at 70 °C for 1 h, and after that, it was allowed to cool down to room temperature for 1 h. The resulting solution of 1-dodeca-3,5-dienylmagnesium bromide (**10**, ~0.5M in THF, 2.00 mL, 1.00 mmol, 2.5 equiv) was slowly added at -78 °C to a solution of the sulfinyl imine *ent*-**1a** (0.102 g, 0.40 mmol) in dry toluene (3.00 mL). The reaction was allowed to reach room temperature over 15 h. After that, it was cooled down to 0 °C, hydrolyzed with water (10 mL) and extracted with EtOAc (3 × 15 mL). The organic layers were dried over magnesium sulfate, and concentrate under vacuum (15 Torr). The residue was purified by flash column chromatography on silica gel using hexane/EtOAc (5:1), affording **11** as a yellow oil; yield: 0.088 g (65%); R_f= 0.50 (hexane/EtOAc 2:1).

$[\alpha]^{20}_D$: +10.9 (*c* 0.98, CH_2Cl_2).

IR (neat): 2923, 2861, 1457, 1361, 1068, 987 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 6.08-5.92 (m, 2H), 5.63-5.49 (m, 2H), 3.69-3.60 (m, 1H), 3.51-3.42 (m, 1H), 3.17-3.10 (m, 1H), 2.17-1,97 (m, 4H), 1.88-1.75 (m, 4H), 1.64-1.46 (m, 2H), 1.42-1.31 (m, 2H), 1.32-1.21 (m, 6H), 1.19 (s, 9H), 0.91-0.84 (m, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 133.2 (CH), 131.1 (CH), 130.9 (CH), 130.1 (CH), 58.5 (CH), 57.5 (C), 48.5 (CH_2), 34.2 (CH_2), 32.7 (CH_2), 31.8 (CH_2), 30.8 (CH_2), 30.0 (CH_2), 29.5 (CH_2), 29.0 (CH_2), 24.4 (CH_2), 23.7 (CH_3), 22.8 (CH_2), 14.2 (CH_3).

MS (EI): *m*/z (%) = 339 (M^+, 0.01%), 266 (23), 235 (77), 234 (100), 192 (15), 164 (20), 150 (49), 137 (25), 136 (17), 124 (23), 118 (42), 110 (48), 96 (29), 83 (17), 70 (42), 67 (18), 57 (24).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{16}H_{28}N$ [M^+-C_4H_9OS]: 234.2222; found: 234.2227.

(+)-Villatamine B {(*S*)-2-[(3*E*,5*E*)-Dodeca-3,5-dien-1-yl]-*N*-ethylpyrrolidine (12)}

To a solution of compound **11** (0.066 g, 0.19 mmol) in MeOH (2.00 mL) was added a 2M solution of HCl in Et_2O (0.95 mL, 1.90 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 30 min. After that, solvents were evaporated (15 Torr), and the resulting residue was dissolved in MeOH (1.30 mL). Acetaldehyde (0.11 mL, 1.90 mmol, 10.0 equiv) and $NaBH_4$ (0.070 g, 1.90 mmol, 10.0 equiv) were added to the methanolic solution, and it was stirred for 15 h at room temperature. After that solvents were evaporated (15 Torr), and a 2M aqueous solution of NaOH (2.00 mL) and CH_2Cl_2 (2.00 mL) were added to the residue. The mixture was stirred for 2 h, and after that, layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 5 mL). The combined organic layers were dried over magnesium sulfate, and concentrate under vacuum (15 Torr). The residue was not purified, affording **12** as a yellow oil; yield: 0.049 g (98%); R_f = 0.58 (CH_2Cl_2/MeOH 10:1).

$[\alpha]^{20}_D$: +45.1 (*c* 0.45, MeOH) [lit.[14] $[\alpha]^{20}_D$: +55.2 (*c* 0.41, MeOH)].

IR (neat): 3016, 2923, 2857, 2788, 1454, 1195, 983, 725 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 6.12-5.84 (m, 2H), 5.66-5.45 (m, 2H), 3.21-3.13 (m, 1H), 2.93-2.82 (m, 1H), 2.21-1.86 (m, 7H), 1.81-1,63 (m, 4H), 1.51-1.41 (m, 2H), 1.40-1.31 (m, 2H), 1.30-1.25 (m, 6H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.91-0.85 (m, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 132.8 (CH), 132.0 (CH), 130.4 (CH), 130.3 (CH), 64.6 (CH), 53.7 (CH_2), 48.3 (CH_2), 34.0 (CH_2), 32.7 (CH_2), 31.9 (CH_2), 30.6 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 22.7 (CH_2), 22.0 (CH_3), 14.2 (CH_3), 13.8 (CH_3).

MS (EI): *m*/z (%) = 263 (M^+, 2.53%), 192 (8), 124 (26), 111 (10), 98 (100), 70 (6).

Reaction of β-Keto Acids 13 with Sulfinyl Imine 1a; General Procedure

To a solution of the corresponding β-keto acid **13** (0.30 mmol) in THF (2.00 mL) was added a 1M solution of LiOEt in THF (0.40 mL, 0.40 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature, and then the imine **1a** (0.051 g, 0.20 mmol) was added and stirring was continued for 8 h at the same temperature. The resulting mixture was hydrolyzed with H_2O (10 mL), and extracted with AcOEt (3 × 15 mL). The organic phase was dried over magnesium sulfate, and the solvent evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc: 1/2) to yield pure compounds **14**.

(4*S*,*S*$_S$)-*N*-(*tert*-Butanesulfinyl)-4-amino-7-bromoheptan-2-one (14a)

Purification by flash column chromatography on silica gel using hexane/EtOAc (1:2) afforded **14a** as a colorless oil; yield: 0.053 g (85%); R_f= 0.18 (hexane/EtOAc 1:3).

$[\alpha]^{20}_D$: +39.0 (*c* 1.23, CH_2Cl_2).

IR (neat): 3217, 2958, 1709, 1415, 1365, 1254, 1049, 895, 733 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 4.06 (d, *J* = 9.4 Hz, 1H), 3.57-3.47 (m, 1H), 3.41 (t, *J* = 6.6 Hz, 2H), 2.99-2.78 (m, 2H), 2.16 (s, 3H), 2.07-1.95 (m, 1H), 1.95-1.84 (m, 1H), 1.84-1.59 (m, 2H), 1.21 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 208.0 (C), 56.0 (C), 53.3 (CH), 49.1 (CH_2), 34.2 (CH_2), 33.3 (CH_2), 31.1 (CH_3), 29.6 (CH_2), 22.7 (CH_3).

MS (EI): *m*/z (%) = 257 (M^+-C_4H_8, 17%), 255 (17), 199 (100), 197 (98), 158 (18), 70 (23), 57 (64), 43 (46), 41 (18).

HRMS (ESI-TOF): *m*/*z* calcd for $C_7H_{13}NO_2S$ [M^+-C_4H_8Br]: 175.0667; found: 175.0672.

(3*S*,*S*$_S$)-*N*-(*tert*-Butanesulfinyl)-3-amino-6-bromo-1-(3,4-dimethoxyphenyl)hexan-1-one (14b)

Purification by flash column chromatography on silica gel using hexane/EtOAc (1:2) afforded **14b** as a yellow oil; yield: 0.071 g (82%); R_f = 0.17 (hexane/EtOAc 1:3).

$[\alpha]^{20}_D$: +36.6 (*c* 0.93, CH_2Cl_2).

IR (neat): 3270, 2950, 1666, 1589, 1516, 1458, 1415, 1358, 1261, 1157, 1022, 872, 810, 760 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.58 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.50 (d, *J* = 2.0 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 4.23 (d, *J* = 9.1 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.80-3.64 (m, 1H), 3.49-3.26 (m, 4H), 2.16-1.99 (m, 1H), 2.02-1.84 (m, 1H), 1.83-1.72 (m, 2H), 1.23 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 197.8 (C), 153.8 (C), 149.2 (C), 130.25 (C), 123.1 (CH), 110.2 (CH), 56.2 (CH_3), 56.2 (CH_3), 56.1 (CH), 54.1 (CH), 44.0 (CH_2), 34.4 (CH_2), 33.4 (CH_2), 29.8 (CH_2), 22.9 (CH_3).

MS (EI): *m*/z (%) = 379 (M^+-C_4H_8, 5%), 377 (5), 297 (12), 181 (32), 180 (31), 166 (11), 165 (100), 117 (63), 70 (21), 57 (24).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{14}H_{20}{}^{79}BrNO_4S$ [M^+-C_4H_8]: 377.0296; found: 377.0305.

(−)-Norhygrine·HCl (15·HCl)

To a solution of compound **14a** (0.047 g, 0.15 mmol) in MeOH (2.00 mL) was added a 2M solution of HCl in Et_2O (0.75 mL, 1.50 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 30 min. After that, solvents were evaporated (15 Torr), and the resulting residue was dissolved in CH_2Cl_2 (3.00 mL). Then, a saturated $NaHCO_3$ aqueous solution was added, and the reaction mixture was stirred at room temperature for 15 h, and after that, layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 5 mL). The combined organic layers containing (−)-norhygrine [GC-MS.- single peak, *m*/*z* 127 (M^+, 6%)] was treated with a 2M HCl solution in Et_2O (0.5 mL, 1.0 mmol) for 15 min and after that the solvents were evaporated (15 Torr) to yield (−)-norhygrine hydrochloride (**15**·HCl) as a white solid; yield: 0.0194 g (79%).

$[\alpha]^{20}_D$ −19.1 (*c* 0.63, EtOH)

IR (neat): 3394, 2915, 1708, 1369 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.47 (s, 1H), 8.24 (s, 1H), 3.97-3.77 (m, 1H), 3.41-3.25 (m, 3H), 2.91 (dd, *J* = 18.6, 5.9 Hz, 1H), 2.25-2.18 (m, 1H), 2.18 (s, 3H), 2.04-1.87 (m, 2H), 1.68-1.55 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 205.9 (C), 55.2 (CH), 45.4 (CH_2), 45.1 (CH_2), 30.5 (CH_2), 30.2 (CH_3), 23.8 (CH_2).

(−)-*trans*-Dendrochrysanine (16)

To a solution of compound **14a** (0.047 g, 0.15 mmol) in MeOH (2.00 mL) was added a 2M solution of HCl in Et_2O (0.75 mL, 1.50 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 30 min. After that, solvents were evaporated (15 Torr), and the resulting residue was dissolved in CH_2Cl_2 (3.00 mL). Then, a saturated $NaHCO_3$ aqueous solution was added, and the reaction mixture was stirred at room temperature for 15 h, and after that, layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). To the combined organic layers containing (−)-norhygrine was successively added a solution of cinnamyl chloride (0.046 g, 42.0 µL, 0.30 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 0.0037 g, 0.03 mmol) in CH_2Cl_2, and Et_3N (0.030 g, 42.0 µL, 0.30 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 16 h. After that, it was hydrolyzed with water (10 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were dried over magnesium sulfate, and concentrate under vacuum (15 Torr). The residue was purified by flash column chromatography on silica gel using hexane/EtOAc (2:1), affording **16** as a yellow wax; 91.5:8.5 er [GC (CP-Chirasil-Dex CB column, $T_{injector}$= 275 °C, $T_{detector}$= 250 °C, T_{column}= 100 °C (10 min) and 100-200 °C (2.5 °C/min), P = 101 kPa): t_{major} = 38.45 min, t_{minor} = 38.76 min]; yield: 0.0296 g (77%); R_f = 0.28 (hexane/EtOAc 1:1).

$[\alpha]^{20}_D$: −17.2 (*c* 1.00, CH_2Cl_2) [lit.[26] $[\alpha]_D^{20}$: −11.8 (*c* = 0.15, $CHCl_3$)].

IR (neat): 2962, 2875, 1708, 1647, 1597, 1415, 1369, 1153, 1061, 976, 764, 702 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.68 (d, *J* = 15.5 Hz, 1H), 7.51 (d, *J* = 1.8 Hz, 2H), 7.40-7.33 (m, 3H), 6.71 (d, *J* = 15.5 Hz, 1H), 4.64-4.58 (m, 0.2H, minor atropoisomer), 4.56-4.46 (m, 0.8H, major atroisomer), 3.74-3.55 (m, 2H), 3.27 (dd, *J* = 16.4, 3.5 Hz, 0.8H, major atropoisomer), 2.77-2.74 (m, 0.4H, minor atropoisomer), 2.46 (dd, *J* = 16.4, 9.3 Hz, 0.8H, major atropoisomer), 2.19 (s, 3H), 2.18 (s, 1H), 2.02 – 1.93 (m, 2H), 1.82 – 1.69 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 207.3 (C), 164.9 (C), 142.2 (CH), 135.3 (C), 129.6 (CH), 128.8 (CH), 127.9 (CH), 118.9 (CH), 54.0 (CH_3), 53.1 (CH), 47.2 (CH_2), 47.1 (CH_2), 30.4 (CH_2), 24.1 (CH_2).

MS (EI): *m*/z (%) = 200 (M^+-CH_2COCH_3, 2%), 132 (12), 131 (100), 126 (16), 103 (34), 102 (6), 84 (21), 77 (17), 70 (6).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{16}H_{19}NO_2$ [M^+]: 257.1416; found: 257.1419.

(−)-Ruspolinone (17)

To a solution of compound **14b** (0.15 mmol) in MeOH (1.50 mL) was added a 2M solution of HCl in Et_2O (0.75 mL, 1.50 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 30 min. After that, solvents were evaporated (15 Torr), and the resulting residue was dissolved in CH_2Cl_2 (4.00 mL). A 2M aqueous solution of NaOH (2.00 mL) was slowly added at 0 ºC, and the reaction mixture was stirred for 2 h at the same temperature. Then the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 8 mL). The combined organic layers were dried over magnesium sulfate, and concentrate under vacuum (15 Torr). The residue was not purified, affording **17** as a colorless wax; 98.5:1.5 er [GC (CP-Chirasil-Dex CB column, $T_{injector}$= 275 ºC, $T_{detector}$= 250 ºC, T_{column}= 100 ºC (10 min) and 100-200 ºC (2.5 ºC/min), P = 101 kPa): t_{minor} = 33.24 min, t_{major} = 33.59 min]; yield: 0.0343 g (92%); R_f = 0.25 (CH_2Cl_2/MeOH 10:1).

$[\alpha]^{20}_D$: −20.2 (*c* 0.79, CH_2Cl_2) [lit.[19b] for (−)-ruspolinone $[\alpha]_D^{20}$: −29.7 (*c* = 0.74, CH_2Cl_2)].

IR (neat): 2950, 2873, 1666, 1589, 1512, 1458, 1415, 1260, 1150, 1018, 876, 810, 760 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.59 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.66-3.51 (m, 1H), 3.15 (dd, *J* = 6.4, 4.9 Hz, 2H), 3.11-2.88 (m, 2H), 2.76 (s, 1H), 2.09-1.93 (m, 1H), 1.96-1.70 (m, 2H), 1.53-1.37 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.2 (C), 153.4 (C), 149.1 (C), 130.5 (C), 122.9 (CH), 110.2 (CH), 110.1 (CH), 56.15 (CH_3), 56.1 (CH_3), 55.0 (CH), 46.25 (CH_2), 44.5 (CH_2), 31.4 (CH_2), 24.8 (CH_2).

MS (EI): *m*/z (%) = 180 (M^+-C_4H_7N, 55%), 166 (11), 165 (100), 137 (11), 122 (7), 79 (10), 77 (10), 51 (5).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{14}H_{19}NO_3$ [M^+]: 249.1365; found: 249.1360.

(4*S*,*S*$_S$)-*N*-(*tert*-Butanesulfinyl)-4-amino-7-chloroheptan-2-one (18)

To a solution of β-keto acid **13a** (0.031 g, 0.30 mmol) in THF (2.00 mL) was added a 1M solution of LiOEt in THF (0.40 mL, 0.40 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature, and then the imine **1b** (0.042 g, 0.20 mmol) was added and stirring was continued for 8 h at the same temperature. The resulting mixture was hydrolyzed with H_2O (10 mL), and extracted with AcOEt (3 × 15 mL). The organic phase was dried over magnesium sulfate, and the solvent evaporated (15 Torr). The residue was purified by flash column chromatography on silica gel using hexane/EtOAc (1:2), affording **18** as a yellow oil; yield: 0.0434 g (81%); R_f= 0.18 (hexane/EtOAc 1:3).

$[\alpha]^{20}_D$: +43.0 (*c* 1.21, CH_2Cl_2)

IR (neat): 3218, 2958, 1709, 1411, 1363, 1266, 1049, 894, 729 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.02 (d, *J* = 9.2 Hz, 1H), 3.47 (t, *J* = 6.2 Hz, 3H), 2.92-2.70 (m, 2H), 2.09 (s, 3H), 1.91-1.74 (m, 1H), 1.70 (m, 3H), 1.14 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 208.2 (C), 56.1 (C), 53.45 (CH), 49.2 (CH_2), 44.7 (CH_2), 33.0 (CH_2), 31.1 (CH_3), 29.5 (CH_2), 22.8 (CH_3).

MS (EI): *m*/z (%) = 211 (M^+-C_4H_8, 15%), 155 (37), 153 (100), 147 (12), 57 (49), 43 (33), 41 (17).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{11}H_{22}{}^{35}ClO_2S$ (M^+): 257.1416; found: 257.1419.$C_{16}H_{19}NO_2$ [M^+]: 257.1416; found: 257.1419.

$C_7H_{13}{}^{35}ClNO$ (M^+ – C_4H_9SO]: 162.0686; found: 162.0691 esto es lo correcto (Galley proofs)

C7H13ClN

(4*R*,*R*$_S$)-*N*-(*tert*-Butanesulfinyl)-4-amino-7-chloroheptan-2-one (*ent*-18)

Starting from chloro imine *ent*-**1b**, and after purification by flash column chromatography on silica gel using hexane/EtOAc (1:2) afforded *ent*-**18** as a yellow oil; yield: 0.0434 g (81%). Physical and spectroscopical data were found to be the same as for **18**.

$[\alpha]^{20}_D$: −41.6 (*c* 1.47, CH_2Cl_2).

Reaction of β-Keto Amine Derivatives 18 with Aldehydes; General Procedure

To a solution of the corresponding β-keto amine derivative **18** (0.039 g, 0.15 mmol) in MeOH (1.50 mL) was added a 2M solution of HCl in Et_2O (0.75 mL, 1.50 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 30 min. After that, solvents were evaporated (15 Torr), and to the resulting residue was successively added L-proline (0.0035 g, 0.03 mmol), $MgSO_4$ (0.018 g, 0.15 mmol), EtOH (1.50 mL), Et_3N (0.016 g, 28.0 µL, 0.15 mmol) and the corresponding aldehyde (0.15 mmol: 0.011 g, 13.75 µL, for *n*-butanal; 0.017 g, 21.0 µL, for heptanal). The resulting mixture was stirred for 6 h at room temperature. Then, it was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ (8.00 mL), and extracted with AcOEt (3 × 15 mL). The organic phase was extracted with 0.15M HCl (3 × 15 mL), and the resulting acidic aqueous phase was basified with a 1M NaOH aqueous solution (pH 9-10), and extracted with AcOEt (3 × 15 mL). The new organic phase was dried with anhydrous magnesium sulfate, and the solvent evaporated (15 Torr). The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH: 95/1) to yield pure compounds **19**.

(5*R*,8a*S*)-5-Propylhexahydroindolizin-7(1*H*)-one (19a)

Purification by flash column chromatography on silica gel using CH_2Cl_2/MeOH (95/1) afforded **19a** as a yellow oil; 98:2 er [GC (CP-Chirasil-Dex CB column, $T_{injector}$= 275 °C, $T_{detector}$= 250 °C, T_{column}= 100 °C (10 min) and 100-200 °C (2.5 °C/min), P = 101 kPa): t_{minor} = 30.77 min, t_{major} = 31.25 min]; yield: 0.0155 g (57%); R_f= 0.17 (CH_2Cl_2/MeOH 99:1).

$[\alpha]^{20}_D$: −22.7 (*c* 0.90, CH_2Cl_2).

IR (neat): 2958, 2873, 2792, 1712, 1458, 1373, 1053, 806, 733 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.28 (td, *J* = 8.8, 2.5 Hz, 1H), 2.50 (dd, *J* = 11.0, 2.1 Hz, 1H), 2.43-2.20 (m, 5H), 2.13 (q, *J* = 8.9 Hz, 1H), 2.01-1.87 (m, 2H), 1.85-1.76 (m, 1H), 1.73-1.62 (m, 1H), 1.60-1.50 (m, 1H), 1.49-1.34 (m, 2H), 1.31-1.16 (m, 1H), 0.93 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 209.6 (C), 64.1 (CH), 61.2 (CH), 50.4 (CH_2), 47.3 (CH_2), 45.8 (CH_2), 37.2 (CH_2), 30.9 (CH_2), 21.6 (CH_2), 18.3 (CH_2), 14.4 (CH_3).

MS (EI): *m*/z (%) = 138 (M^+-C_3H_7, 100%), 124 (20), 110 (9), 97 (10), 96 (100), 70 (10), 68 (7), 55 (7), 54 (6).

HRMS (ESI-TOF): *m*/*z* calcd for $C_8H_{12}NO$ [M^+-C_3H_7]: 138.0919; found: 138.0924.

(5*S*,8a*R*)-5-Propylhexahydroindolizin-7(1*H*)-one (*ent*-19a)

Starting from β-keto amine derivative *ent*-**18**, and after purification by flash column chromatography on silica gel using CH_2Cl_2/MeOH (95/1) afforded *ent*-**19a** as a yellow oil; 98.5:1.5 er [GC (CP-Chirasil-Dex CB column, $T_{injector}$= 275 °C, $T_{detector}$= 250 °C, T_{column}= 100 °C (10 min) and 100-200 °C (2.5 °C/min), P = 101 kPa): t_{major} = 30.74 min, t_{minor} = 31.40 min]; yield: 0.0149 g (55%). Physical and spectroscopical data were found to be the same as for **19a**.

$[\alpha]^{20}_D$: +21.1 (*c* 0.44, CH_2Cl_2).

(5*R*,8a*S*)-5-Hexylhexahydroindolizin-7(1*H*)-one (19b)

Purification by flash column chromatography on silica gel using CH_2Cl_2/MeOH (95/1) afforded **19b** as a yellow oil; 95.5:4.5 er [GC (CP-Chirasil-Dex CB column, $T_{injector}$= 275 °C, $T_{detector}$= 250 °C, T_{column}= 100 °C (10 min) and 100-200 °C (2.5 °C/min), P = 101 kPa): t_{major} = 38.49 min, t_{minor} = 38.88 min]; yield: 0.0178 g (53%); R_f= 0.17 (CH_2Cl_2/MeOH 99:1).

$[\alpha]^{20}_D$: −17.8 (*c* 0.40, CH_2Cl_2).

IR (neat): 2927, 2862, 2781, 1720, 1458, 1373, 1053, 968, 798 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.29 (td, *J* = 8.8, 2.5 Hz, 1H), 2.55-2.45 (m, 1H), 2.42-2.21 (m, 3H), 2.14 (q, *J* = 9.0 Hz, 1H), 2.03-1.86 (m, 2H), 1.88-1.76 (m, 1H), 1.75-1.64 (m, 1H), 1.63-1.51 (m, 1H), 1.51-1.40 (m, 1H), 1.35-1.18 (m, 10H), 0.89 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 209.7 (C), 64.1 (CH), 61.3 (CH), 50.4 (CH_2), 47.3 (CH_2), 45.8 (CH_2), 34.9 (CH_2), 31.9 (CH_2), 30.9 (CH_2), 29.6 (CH_2), 25.0 (CH_2), 22.7 (CH_2), 21.6 (CH_2), 14.2 (CH_3).

MS (EI): *m*/z (%) = 138 (M^+-C_5H_7, 100%), 139 (17), 138 (100), 97 (6), 96 (77), 68 (5), 55 (5).

HRMS (ESI-TOF): *m*/*z* calcd for $C_8H_{12}NO$ [M^+-C_6H_{13}]: 138.0919; found: 138.0920.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

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Biosketches

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Francisco Foubelo was born in 1961 and studied Chemistry at the University of Oviedo where he received B.S. (1984), M.S. (1986) and Ph.D. (1989) degrees, under the direction of Professors J. Barluenga, M. Yus and F. J. Fañanás. He then joined the laboratory of Professor M. F. Semmelhack at Princeton University as a Fulbright postdoctoral fellow, and, in 1991, the group of Professor M. Yus at the University of Alicante, where he became an associate professor in 1995, and a full professor in 2002. His current research interests are focused on the development of new synthetic methodologies involving chiral sulfinyl imines, and on metal-promoted functionalization of alkenes and alkynes.