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A new asymmetric synthesis of 2,6-*cis*-disubstituted 4-methylenepiperidines: total synthesis of (+)-alkaloid 241D and (+)-isosolenopsin A

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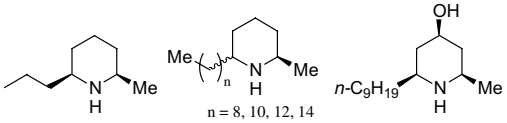
Abstract—A highly diastereoselective synthesis of 2,6-*cis*-disubstituted-4-methylenepiperidines based on a Mannich type intramolecular cyclization of an allylsilane on an iminium ion is described. The synthetic potential of this methodology is demonstrated by the enantioselective synthesis of two natural piperidine alkaloids: (+)-alkaloid 241D and (+)-isosolenopsin A.

1. Introduction

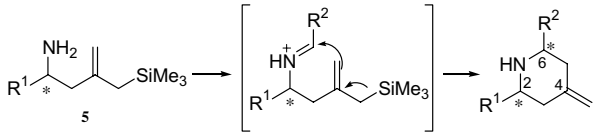
Many natural biologically active compounds contain the piperidine ring system as a common structural element. Among the numerous piperidines, *cis*- and *trans*-2,6-dialkylpiperidines represent an important class of alkaloids isolated from insects, amphibians or plants.[1] For instance, dihydropinidine **1** was found in the Mexican beetle *Epilachna varivestis*.[2] Solenopsins **2** and isosolenopsins **3** are extracted from the fire ants' venom of the genus *Solenopsis*,[3] while alkaloid 241D **4** was isolated from the poison frog Dendrobates[4] (Fig. 1).

The stereoselective synthesis of piperidines, and notably 2,6-*cis*-disubstituted piperidines, has received considerable attention[5,6] due to the broad range of their biological activity.[7] As part of our programme to expand the synthetic utility of allylsilyl-functionalized substrates for the synthesis of natural products,[8] we have applied this strategy to the synthesis of these compounds. In this case, the piperidine ring would be formed by a Mannich type intramolecular cyclization reaction starting from substituted aminoallylsilanes **5** (Scheme 1).



1 2 (*trans*); 3 (*cis*) 4

Figure 1. Examples of natural piperidines.



Scheme 1. Formation of the piperidine ring by intramolecular addition of an allylsilane on an iminium ion.

2. Results and discussion

Previously,[9] we have described the enantioselective synthesis of substrates **5**. They were prepared from α,β-ethylenic esters **6** in four steps in 21–67% overall yields and 80–84% enantiomeric excesses (Scheme 2).

2.1. Synthesis of 2,6-disubstituted-4-methylenepiperidines

Since numerous natural piperidines are substituted by a methyl group at the 2 position, we have chosen to prepare piperidines **17**–**22** by condensation of methyl substituted aminoallylsilane (*R*)-**5a** on carbonyl compounds **11**–**16** (Scheme 3).

Reaction of aminoallylsilane (*R*)-**5a** (ee = 82%) with aldehydes **11**–**15** in the presence of trifluoroacetic acid

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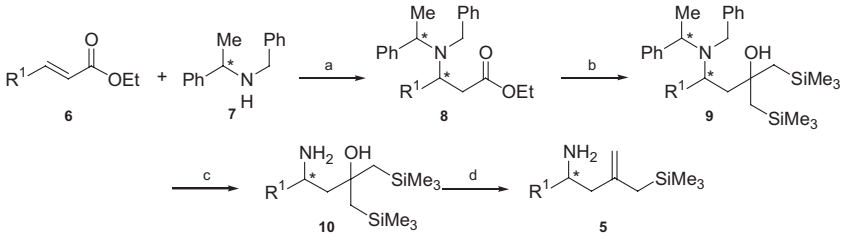
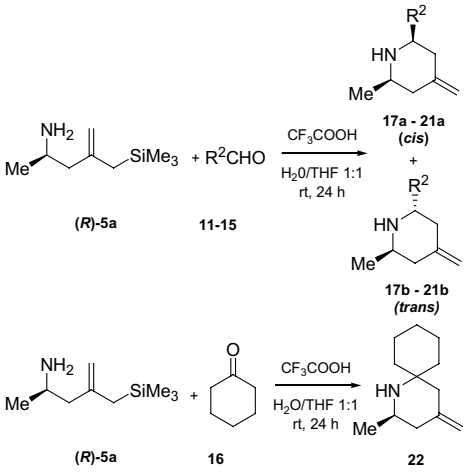


Scheme 2. Reagents and conditions: (a) *n*-BuLi, THF, 0 °C; (b) $Me_3SiMgCl$ then $CeCl_3$, THF, rt, 3 days; (c) $Pd(OH)_2$, H_2, MeOH, H_2O, THF, AcOH, 24 h; (d) HCl 1 M, diethyl ether, 1–24 h.



Scheme 3. Synthesis of 4-methylenepiperidines from aminoallylsilane (*R*)-**5a**.

in a mixture of water–THF (1:1) at room temperature for 24 h led to a mixture of *cis*- and *trans*-4-methylenepiperidines. The results are summarized in Table 1. In all cases, the *cis*-diastereomers were predominant. The diastereoisomeric excesses, which were found to be better than 82%, were determined by ^{1}H NMR spectroscopy on the signals corresponding to the methylene protons. The relative configuration of the *cis*-diastereoisomers **17a**–**21a** was established unambiguously by ^{1}H NMR spectroscopy. For instance, the ^{1}H NMR spectrum of **21a** showed triplets for H-3$_{ax}$ and H-5$_{ax}$ with $J = 12.8$ Hz and $J = 12.9$ Hz corresponding, respectively, to geminal and *trans*-diaxial couplings indicative of a *cis*-stereochemistry for the 2,6-disubstituted piperidine ring. These results were confirmed by NOE experiments on isomers **21a** and **21b** (Fig. 2).

To explain such a diastereoselectivity, we considered the transition states **A** and **B** (Scheme 4). It appears that the transition state **B** leading to the 2,6-*trans* isomer is disfavoured due to a 1,3-diaxial interaction compared to the transition state A leading to the 2,6-*cis* isomer.

The enantiomeric purity of piperidines **18a**–**21a** and **22** was determined using two different techniques: GC–MS with Mosher's acid derivatives and ^{1}H NMR with (*R*)-mandelic acid derivatives. The results (Table 1) have shown that a partial racemization occurred during the cyclization step. This racemization can be explained by an aza-Cope type rearrangement. It has already been observed previously by other authors[10] during the addition of vinyl and allylsilanes on iminium salts.

In order to improve yields and minimize racemization during the cyclization step, we studied the preparation of piperidines **17**–**22** from β-aminohydroxysilanes **10**, precursors of β-aminoallylsilanes **5** (Scheme 5).

Reaction of β-aminohydroxysilanes **10** with carbonyl derivatives **11**, **13**–**16** and **23** in the presence of trifluoroacetic acid (10 equiv) in a mixture of water–THF (1:1) at room temperature for 3 days led to a mixture of *cis*- and *trans*-4-methylenepiperidines. The results are summarized in Table 2.

As in the preceding results, in all cases, the *cis*-diastereoisomers were predominant. Comparison of these results with those mentioned in Table 1 shows that diastereoselectivity is about the same but enantioselectivity is significantly increased when the piperidine ring is achieved from aminohydroxysilanes.

A mechanism that could account for the formation of 4-methylenepiperidines from β-aminohydroxysilanes **10** is depicted in Scheme 6. Cyclization might proceed by the following sequence: after formation of 1,3-oxazinane **24** and its protonation, iminium ion **25** is generated. Protonation of the oxygen atom leads to allylsilane **26** and finally cyclization affords the expected piperidine. In this case, the allylsilane moiety is generated in situ and reacts instantaneously with the iminium ion previously formed.

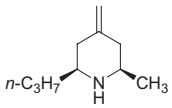
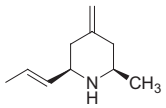
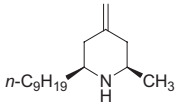
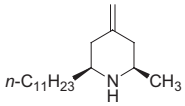
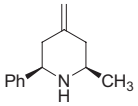
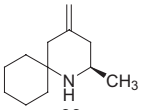
The intermediate 1,3-oxazinanes **24** were unambiguously displayed by isolation of **24a** (R^1 = Me, R^2 = *n*-C_9H_{19}) and **24b** (R^1 = Me, R^2 = Ph) from, respectively, condensation of decanal **13** and benzaldehyde **15** with β-aminohydroxysilane (*R*)-**10a** without adding trifluoroacetic acid. Furthermore, treatment of **24a** with trifluoroacetic acid led to piperidine **19a**.

2.2. Total synthesis of piperidine alkaloids

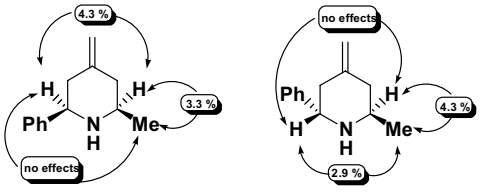
The preceding results have shown that the best way to access to 4-methylenepiperidines is from β-aminohydroxysilanes **10**. We have used this strategy for the total synthesis of piperidine alkaloids (+)-alkaloid 241D **4** and (+)-isosolenopsin A **3a**.

2.2.1. Synthesis of (+)-alkaloid 241D 4. Racemic alkaloid 241D was shown to have interesting biological activ-

Table 1. Preparation of 4-methylenepiperidines from aminoallylsilane **5a**

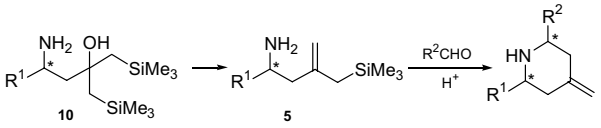
Carbonyl compound	Major product	De[a] (%)	Yield[b] (%)	Ee[b] (%)
n-C_3H_7CHO **11**	 **17a**	84	49	n.d. ($[\alpha]_D^{21} = -4$)
$CH_3CH{=}CHCHO$ **12**	 **18a**	n.d.	32	78[c]
n-$C_9H_{19}CHO$ **13**	 **19a**	84	49	28[d]
n-$C_{11}H_{23}CHO$ **14**	 **20a**	82	58	38[d]
PhCHO **15**	 **21a**	86	70	76[d]
 **16**	 **22**	86	46	24[c]

[a] Determined by ^1H NMR on the crude product.
[b] Determined on the major isolated piperidine.
[c] Determined by ^1H NMR of the (*R*)-mandelic acid ammonium salt.
[d] Determined by GC–MS of the Mosher's acid derivative.



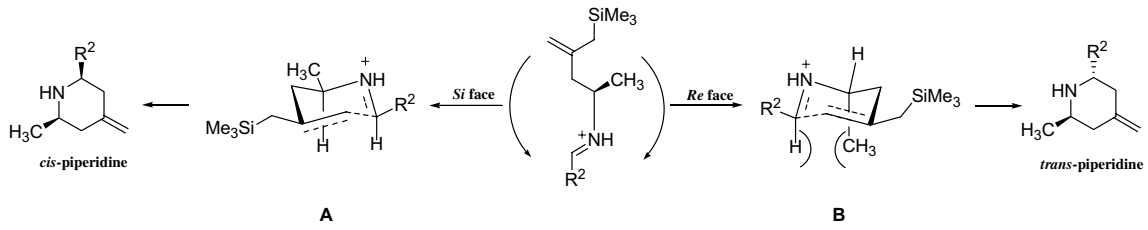
21a (*cis*) **21b** (*trans*)

Figure 2. NOE effects on *cis*- and *trans*-piperidines **21**.



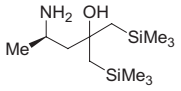
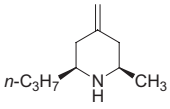
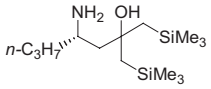
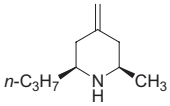
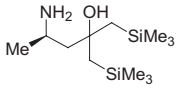
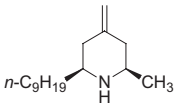
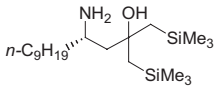
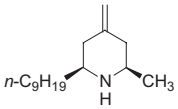
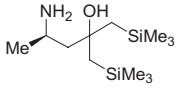
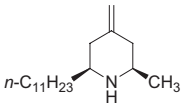
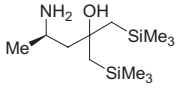
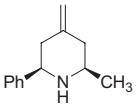
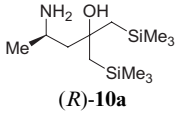
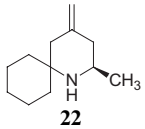
Scheme 5. Synthesis of 4-methylenepiperidines from β-aminohydroxyallylsilanes **10**.

ities: for example, it stops the action of acetylcholine by a noncompetitive blocker of the nicotinic receptor channel complex.[11] Also it is a potent inhibitor of binding of [^{3}H]-perhydrohistrionicotoxin to nicotinic receptor channels of electroplax membranes.[12] Various asymmetric synthesis of (+)-alkaloid 241D have been described.[13] We have used methylenepiperidine **19a** to prepare this alkaloid

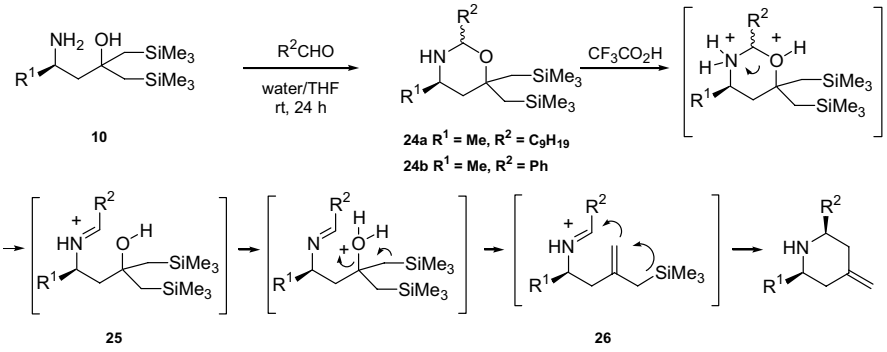


Scheme 4. Explanation of diastereoselectivity.

Table 2. Preparation of 4-methylenepiperidines from β-aminohydroxysilanes **10**

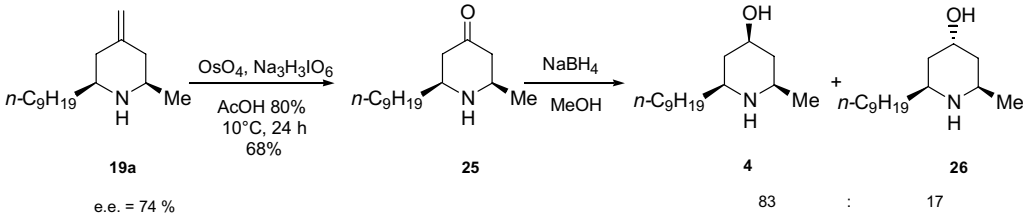
	Aminoalcohol	Carbonyl compound	Major product	De[a] (%)	Yield[b] (%)	Ee[b] (%)
1	 (*R*)-**10a**	*n*-C_3H_7CHO **11**	 **17a**	82	53	n.d. ($[\alpha]_D^{21} = -5.5$)
2	 (*S*)-**10b**	CH_3CHO **23**	 **17a**	82	32	n.d. ($[\alpha]_D^{21} = -5.5$)
3	 (*R*)-**10a**	*n*-$C_9H_{19}CHO$ **13**	 **19a**	84	73	74[d]
4	 (*S*)-**10c**	CH_3CHO **23**	 **19a**	78	53	76[d]
5	 (*R*)-**10a**	*n*-$C_{11}H_{23}CHO$ **14**	 **20a**	84	70	64[d]
6	 (*R*)-**10a**	PhCHO **15**	 **21a**	90	70	84[d]
7	 (*R*)-**10a**	 **16**	 **22**	90	25	14[c]

[a] Determined by ^1H NMR on the crude product.
[b] Determined on the major isolated piperidine.
[c] Determined by ^1H NMR of the (*R*)-mandelic acid ammonium salt.
[d] Determined by GC–MS of the Mosher's acid derivative.

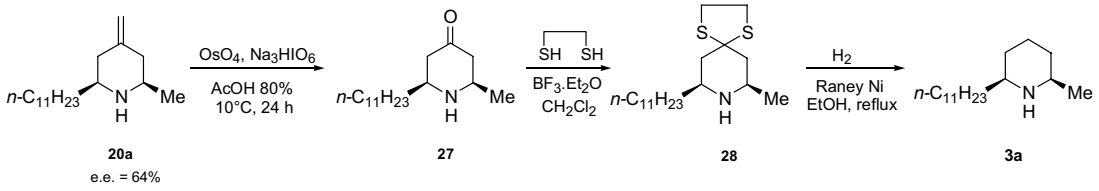


Scheme 6. Mechanism of the formation of 4-methylenepiperidines from aminohydroxysilanes **10**.

according to the sequence outlined in Scheme 7. Oxidation of 4-methylenepiperidine **19a** with osmium tetroxide in the presence of $Na_3H_3IO_6$ in acetic acid led to piperidin-4-one **25** in 68% yield. The stereoselective reduction



Scheme 7. Synthesis of (+)-alkaloid 241D **4**.



Scheme 8. Synthesis of the (+)-isosolenopsin A hydrochloride **3a**.

of **25** with sodium borohydride afforded (+)-alkaloid 241D **4** and its C-4 epimer **26** in a ratio of 83:17. The natural product was isolated in a 66% yield. Consequently, (+)-alkaloid 241D was obtained in six steps from methyl crotonate in an overall yield of 23% and an enantiomeric excess of 74% {$[\alpha]_D^{25} = +5.5$ (*c* 1.04, MeOH), lit.[13a] $[\alpha]_D^{25} = +6.5$ (*c* 2, MeOH)}.

2.2.2. Synthesis of (+)-isosolenopsin A 3a. (+)-Isosolenopsin A has been shown to have numerous biological activities such as antibacterian, antifongic, insecticide and phytocid. According to a similar sequence, (+)-isosolenopsin A[14] was prepared from 4-methylenepiperidine **20a**. (Scheme 8). Oxidation of **20a** with osmium tetroxide and $Na_3H_3IO_6$ led to piperidin-4-one **27** in 67% yield. Treatment of **27** with an excess of ethane dithiol in the presence of $BF_3{\cdot}Et_2O$ gave the dithiolane derivative **28** in 82% yield. Finally, **28** was converted into (+)-isosolenopsin A **3a** (isolated as its hydrochloride salt) in 43% yield using Raney nickel in reflux ethanol.

(+)-Isosolenopsin A (HCl) was obtained in seven steps from ethyl crotonate in 11% overall yield and 64% enantiomeric excess. {$[\alpha]_D^{25} = +5.5$ (*c* 1.00, $CHCl_3$), lit.[14c] $[\alpha]_D = +10.0$ (*c* 1.17, $CHCl_3$)}.

3. Conclusion

We have described a new approach for the enantioselective synthesis of 2,6-*cis*-disubstituted-4-methylenepiperidines. The key step of the sequence is an intramolecular allylsilane–iminium cyclization. Piperidines were obtained with good yields and excellent diastereoselectivity. Moderate enantiomeric excesses were measured when a β-aminoallylsilane was used as starting material, a better enantioselectivity was observed when we started from β-aminohydroxysilanes. This methodology was applied to the synthesis of (+)-alkaloid 241D and (+)-isosolenopsin A.

4. Experimental

4.1. General

Commercially available materials were used without further purification. THF used for moisture sensitive operations were distilled from potassium/benzophenone under an argon atmosphere. All moisture sensitive reactions were carried out in flame-dried glassware under an argon atmosphere. Analytical thin layer chromatography (TLC) was performed on Merck silica gel $60F_{254}$ plates. Visualization on TLC was achieved by use of UV light (254 nm), iodide, ninhydrin or vanillin followed by heating. Flash chromatography was performed using Merck silica gel 40–60 μm.

Infrared spectra were recorded on a Perkin–Elmer 881 (spectra in solution) or on a Perkin–Elmer FTIR Spectrometer Paragon 500 (film). Only selected absorbances are reported. Optical rotations were measured on a Jasco DIP-370 polarimeter at 589 nm (Na D-line).

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 spectrometer at operating frequencies of 400 MHz (^{1}H NMR) or 100 MHz (^{13}C NMR). Chemical shifts (δ) are given in ppm relative to $CDCl_3$ (δ = 7.27 ppm for ^{1}H, δ = 77.1 ppm for ^{13}C) and coupling constants (*J*) in hertz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, m for multiplet; the prefix br is used for a broad signal.

Mass spectra (MS) in electronic ionization mode (EI) were recorded on an Agilent 6890N mass spectrometer (GC/MS). Other spectra were performed on a Hewlett–Packard 5989B spectrometer. High-resolution mass spectra (HRMS) were recorded at the Centre Régional de Mesures Physique de l'Ouest (CRMPO, University of Rennes I, France) on a Varian Mat 311 spectrometer (EI) or on a Micromass ZABSpecTOF (ESI).

Microanalysis were carried out at the Laboratoire Central de Microanalyse du CNRS (Vernaison, France).

4.2. General procedure for preparation of 8

To a solution of (*R*)- or (*S*)-*N*-benzyl-*N*′-α-methylbenzylamine **7** (1.1 equiv, 0.25–0.32 mol L^{-1}) in dry THF was added dropwise at 0 °C a solution of *n*-butyllithium (1.2 equiv) in hexane (c = 1.6 mol L^{-1}). After stirring for 15 min, a solution of the α,β-ethylenic ester **6** (23–35 mmol, 1.1–1.6 mol L^{-1}) in dry THF was added at 0 °C. After stirring for 1 h, the mixture was hydrolyzed with a saturated solution of ammonium chloride. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (cyclohexane/AcOEt 95:5). A mixture of two diastereoisomers was obtained.

4.2.1. Ethyl (3*R*,3′*R*)-3-(*N*-α-methylbenzyl-*N*′-benzylamino)-butanoate 8a. Pale yellow oil; yield: 83%; TLC: R_f = 0.37 (cyclohexane/AcOEt, 95:5); de = 82%; $[\alpha]_D^{25} = +3$ (c 1.12, $CHCl_3$); IR (CCl_4): ν (cm^{-1}) 1730; ^1H NMR δ major diastereoisomer 1.20 (d, 3H, J = 6.7 Hz), 1.22 (t, 3H, J = 7.1 Hz), 1.41 (d, 3H, J = 6.9 Hz), 2.29 (AB part of ABX system, 2H, $\Delta\nu$ = 100 Hz), δ_A = 2.42 (dd, 1H, J_{AB} = 14.1 Hz, J_{AX} = 6.0 Hz, δ_B = 2.17 (dd, 1H, J_{AB} = 14.1 Hz, J_{BX} = 8.0 Hz)), 3.51 (X part of ABX system, m, 1H, J_{AX} = 6.0 Hz, J_{BX} = 8.0 Hz), 3.77 (AB system, 2H, $\Delta\nu$ = 20 Hz, δ_A = 3.79 (d, 1H, J_{AB} = 14.7 Hz), δ_B = 3.75 (d, 1H, J_{AB} = 14.7 Hz)), 3.92–4.11 (m, 3H), 7.24–7.49 (m, 10H); ^{13}C NMR δ major diastereoisomer 14.2, 18.0, 18.6 (CH_3), 39.9, 49.7 (CH_2), 50.1, 57.9 (CH), 60.2 (CH_2), 126.6, 126.7, 127.8, 128.0, 128.1, 128.2, 128.4 (CH), 141.7, 144.3, 172.5 (C); MS for $C_{21}H_{27}NO_2$: m/z 325. Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.92; H, 8.45; N, 4.07.

4.2.2. Ethyl (3*S*,3′*S*)-3-(*N*-α-methylbenzyl-*N*′-benzylamino)-hexanoate 8b. Yellow oil; yield: 70%; TLC: R_f = 0.33 (cyclohexane/AcOEt, 95:5); de = 82%; $[\alpha]_D^{25} = -20$ (c 1.31, $CHCl_3$); IR (CCl_4): ν (cm^{-1}) 1735; ^1H NMR δ major diastereoisomer 0.78 (t, 3H, J = 7.2 Hz), 1.08 (t, 3H, J = 7.2 Hz), 1.12–1.22 (m, 2H), 1.25 (d, 3H, J = 6.8 Hz), 1.36–1.57 (m, 2H), 1.93 (AB part of ABX system, 2H, $\Delta\nu$ = 20 Hz, δ_A = 1.95 (dd, 1H, J_{AB} = 14.5 Hz, J_{AX} = 4.2 Hz), δ_B = 1.90 (dd, 1H, J_{AB} = 14.6 Hz, J_{BX} = 8.9 Hz)), 3.24 (X part of ABX system, m, 1H, J_{AX} = 4.2 Hz, J_{BX} = 8.9 Hz), 3.57 (AB system, 2H, $\Delta\nu$ = 99 Hz, δ_A = 3.70 (d, 1H, J_{AB} = 14.9 Hz), δ_B = 3.45 (d, 1H, J_{AB} = 14.9 Hz)), 3.74 (q, 1H, J = 7.0 Hz), 3.85–3.99 (m, 2H), 7.10–7.35 (m, 10H); ^{13}C NMR δ major diastereoisomer 14.2, 14.3, 19.8 (CH_3), 20.3, 35.9, 36.9, 50.0 (CH_2), 53.8, 58.0 (CH), 60.1 (CH_2), 126.6, 126.8, 126.9, 127, 128.0, 128.1, 128.2, 128.3 (CH), 143.2, 141.9, 173.0 (C); MS for $C_{23}H_{31}NO_2$: m/z 353. Anal. Calcd for $C_{23}H_{31}NO_2$: C, 78.15; H, 8.84; N, 3.96. Found: C, 78.10; H, 8.65; N, 3.87.

4.2.3. Ethyl (3*S*,3′*S*)-3-(*N*-methylbenzyl-*N*′-benzylamino)-dodecanoate 8c. Yellow oil; yield: 69%; TLC: R_f = 0.48 (cyclohexane/AcOEt, 95:5); de = 80%; $[\alpha]_D^{25} = -11$ (c 1.10, $CHCl_3$); IR (CCl_4): ν (cm^{-1}) 1722; ^1H NMR δ major diastereoisomer 0.95 (t, 3H, J = 6.9 Hz), 1.23 (t, 3H,J = 7.2 Hz), 1.25–1.36 (m, 14H), 1.39 (d, 3H, J = 6.8 Hz), 1.51–1.65 (m, 1H, H-4), 2.08 (AB part of ABX system, 2H, H-2, $\Delta\nu$ = 21 Hz, δ_A = 2.10 (dd, 1H, J_{AB} = 14.4 Hz, J_{AX} = 4.1 Hz), δ_B = 2.05 (dd, 1H, J_{AB} = 14.4 Hz, J_{BX} = 8.7 Hz)), 3.36 (m, 1H), 3.72 (AB system, 2H, $\Delta\nu$ = 99 Hz, δ_A = 3.84 (d, 1H, J_{AB} = 15.0 Hz), δ_B = 3.60 (d, 1H, J_{AB} = 15.0 Hz)), 3.89 (q, 1H, J = 7.0 Hz), 4.0–4.13 (m, 2H), 7.25–7.50 (m, 10H); ^{13}C NMR δ major diastereoisomer 14.3, 19.7 (CH_3), 22.7, 27.0, 29.5, 29.6, 32.0, 33.6, 36.9, 50.0 (CH_2), 54.1, 56.9 (CH), 60.1 (CH_2), 126.8, 126.9, 128.1, 128.7 (CH), 141.8, 143.3, 172.9 (C); MS for $C_{29}H_{43}NO_2$: m/z 465. Anal. Calcd for $C_{29}H_{43}NO_2$: C, 79.59; H, 9.90; N, 3.20. Found: C, 79.76; H, 10.13; N, 3.10.

4.3. General procedure for the preparation of 9

Powdered $CeCl_3{\cdot}7H_2O$ (4.5–4.6 equiv) was dried under vacuum (0.5 mmHg) for 3 days at 120–130 °C while stirring. The flask was flushed with argon, then dry THF (7 mL/g of $CeCl_3{\cdot}7H_2O$) added. The white suspension was stirred at room temperature for an additional 2 h. This slurry was cooled to −78 °C and trimethylsilyl methylmagnesium chloride (4.6 equiv; freshly prepared from trimethylsilylmethyl chloride and magnesium) in dry THF (30 mL) was added dropwise over a period of 1–2 h. The cold mixture was stirred for 1 h and ester **8** (7–10 mmol) in dry THF (10 mL) was added dropwise over 30 min. The resulting mixture was allowed to warm to room temperature and stirred for 3 days. The reaction mixture was then cooled to −10 °C and hydrolyzed by the dropwise addition of 1 M hydrochloric acid. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (cyclohexane/AcOEt 95:5).

4.3.1. (3′*R*,4*R*)-4-(*N*-α-Methylbenzyl-*N*′-benzylamino)-1-trimethylsilyl-2-trimethylsilylmethylpentan-2-ol 9a. Colourless oil; yield: 90%; TLC: R_f = 0.52 (cyclohexane/AcOEt 95:5); de = 82% $[\alpha]_D^{25} = +24$ (c 1.12, $CHCl_3$); IR (CCl_4): ν (cm^{-1}) 3240; ^1H NMR δ major diastereoisomer −0.21 (s, 9H), 0.00 (s, 9H), 0.05 (AB system, 2H, $\Delta\nu$ = 235 Hz, δ_A = 0.35 (d, 1H, J_{AB} = 14.6 Hz), δ_B = −0.24 (d, 1H, J_{AB} = 14.6 Hz)), 0.77 (AB system, 2H, $\Delta\nu$ = 44 Hz, δ_A = 0.82 (d, 1H, J_{AB} = 14.8 Hz), δ_B = 0.72 (d, 1H, J_{AB} = 14.8 Hz)), 1.07 (d, 3H, J = 6.4 Hz), 1.35 (d, 3H, J = 7.2 Hz), 1.48 (AB part of ABX system, 2H, H-3, $\Delta\nu$ = 385 Hz, δ_A = 1.96 (t, J = 13.2 Hz, J_{AX} = 1.6 Hz), δ_B = 1.00 (dd, J_{AB} = 14.4 Hz, J_{BX} = 2.0 Hz)), 3.23–3.32 (X part of ABX system, m, 1H), 3.73 (AB system, 2H, $\Delta\nu$ = 187 Hz, δ_A = 3.97 (d, 1H, J_{AB} = 12.8 Hz), δ_B = 3.50 (d, 1H, J_{AB} = 12.8 Hz)), 3.90 (q, 1H, J = 6.8 Hz), 6.29 (s, 1H), 7.10–7.42 (m, 10H); ^{13}C NMR δ major diastereoisomer 0.4, 1.1, 13.6, 18.6 (CH_3), 33.1, 34.9, 45.8 (CH_2), 48.9 (CH), 49.0 (CH_2), 56.2 (CH), 75.8 (C), 127.4, 128.4, 128.7, 129.1, 129.8 (CH), 139.2, 142.6 (C). Anal. Calcd for $C_{27}H_{45}NOSi_2$:

C, 71.14; H, 9.95; N, 3.07. Found: C, 71.57; H, 10.08; N, 3.10.

4.3.2. (3′*S*,4*S*)-4-(*N*-α-Methylbenzyl-*N*′-benzylamino)-1-trimethylsilyl-2-trimethylsilylmethylheptan-2-ol 9b Yellow oil; yield: 72%; TLC: $R_f = 0.38$ (cyclohexane/AcOEt, 95:5); $[\alpha]_D^{25} = -5$ (*c* 1.04, $CHCl_3$); IR (CCl_4): *v* (cm^{-1}) 3260; ^1H NMR δ major diastereoisomer −0.15 (s, 9H), 0.00 (s, 9H), 0.19 (AB system, 2H, $\Delta v = 158$ Hz, $\delta_A = 0.38$ (d, 1H, $J_{AB} = 14.6$ Hz), $\delta_B = -0.01$ (d, 1H, $J_{AB} = 14.6$ Hz)), 0.86 (AB system, 2H, $\Delta v = 32$ Hz, $\delta_A = 0.90$ (d, 1H, $J_{AB} = 14.6$ Hz), $\delta_B = 0.82$ (d, 1H, $J_{AB} = 14.6$ Hz)), 0.92 (t, 3H, $J = 7.0$ Hz), 1.13–1.32 (m, 2 H), 1.35 (d, 3H, $J = 6.8$ Hz), 1.51 (AB part of ABX system, 2H, $\Delta v = 228$ Hz, $\delta_A = 1.80$ (dd, 1H, $J_{AB} = 14.5$ Hz, $J_{AX} = 11.4$ Hz), $\delta_B = 1.23$ (dd, 1H, $J_{AB} = 14.5$ Hz, $J_{BX} = 2.4$ Hz)), 1.65–1.73 (m, 2H, H-5), 3.09 (X part of ABX system, t, 1H, $J = 10.4$ Hz), 3.75 (AB system, 2H, $\Delta v = 158$ Hz, $\delta_A = 3.95$ (d, 1H, $J_{AB} = 13.1$ Hz), $\delta_B = 3.55$ (d, 1H, $J_{AB} = 13.1$ Hz)), 3.91 (q, 1H, $J = 6.8$ Hz), 6.36 (br s, 1H), 7.11–7.40 (m, 10H, H aromatics); ^{13}C NMR δ major diastereoisomer 0.9, 1.0, 14.7 (CH_3), 21.1, 32.0, 34.9, 35.0, 43.4, 49.5 (CH_2), 54.3, 57.2 (CH), 75.9 (C), 127.3, 128.3, 128.5, 128.6, 128.9, 129.6 (CH), 139.5, 142.7 (C); MS (CI, methane) for $C_{29}H_{49}NOSi_2 + H$: *m*/*z* 484 ($M+H^+$). Anal. Calcd for $C_{29}H_{49}NOSi_2$: C, 71.98; H, 10.21; N, 2.89. Found: C, 72.25; H, 10.30; N, 3.38.

4.3.3. (3′*S*,4*S*)-4-(*N*-α-Methylbenzyl-*N*′-benzylamino)-1-trimethylsilyl-2-trimethylsilylmethyltridecan-2-ol 9c. Yellow oil; yield: 71%; TLC: $R_f = 0.48$ (cyclohexane/AcOEt 95:5); $[\alpha]_D^{25} = -3$ (*c* 0.95, $CHCl_3$); FTIR (film): *v* (cm^{-1}) 3256; ^1H NMR δ major diastereoisomer −0.15 (s, 9H), 0.00 (s, 10H), 0.37 (d, 1H), 0.80–0.92 (m, 5H), 1.10–1.42 (m, 17H), 1.35 (d, 3H, $J = 6.9$ Hz), 1.80 (dd, 1H, $J = 14.3$ Hz, $J = 11.4$ Hz), 3.1 (t, 1H, $J = 9.9$ Hz), 3.75 (AB system, 2H, $\Delta v = 159$ Hz, $\delta_A = 3.95$ (d, 1H, $J_{AB} = 13.1$ Hz), $\delta_B = 3.55$ (d, 1H, $J_{AB} = 13.1$ Hz)), 3.90 (q, 1H, $J = 6.9$ Hz), 6.35 (br s, 1H), 7.13–7.40 (m, 10H); ^{13}C NMR δ major diastereoisomer 0.8, 1.0, 14.1, 14.7 (CH_3), 22.7, 26.9, 27.9, 29.3, 29.6, 32.0, 35.0, 43.4, 49.4 (CH_2), 54.6, 57.2 (CH), 75.9 (C), 127.1, 127.3, 128.3, 128.5, 128.9, 129.6 (CH), 139.5, 142.7 (C); MS (CI, methane) for $C_{35}H_{61}NOSi_2 + H$: *m*/*z* 568 ($M+H^+$). Anal. Calcd for $C_{35}H_{61}NOSi_2$: C, 74.01; H, 10.82; N, 2.47. Found: C, 74.53; H, 11.11; N, 2.65.

4.4. General procedure for preparation of 10

To a solution of **9** (1 g) in methanol (13 mL), acetic acid (0.31 mL), water (2.7 mL) and THF (2.4 mL) was added Pearlman's catalyst (0.3 g). The resulting mixture was stirred under 3.5 atm of hydrogen at room temperature for 24 h in Parr apparatus. The mixture was filtered through Celite and concentrated to give a residue which was treated with sodium hydrogenocarbonate then extracted with methylene chloride and organic layers were dried (K_2CO_3) and evaporated.

4.4.1. (4*R*)-4-Amino-1-trimethylsilyl-2-trimethylsilylmethylpentan-2-ol 10a. Liquid purified by distillation on Kugelrohr: 172 °C/0.5 mmHg; yield: 92%; TLC: $R_f = 0.18$ (AcOEt); $[\alpha]_D^{25} = +1$ (*c* 1.18, $CHCl_3$); IR (CCl_4): *v* (cm^{-1}) 3260; ^1H NMR 0.03 (s, 1H), 0.06 (s, 1H), 1.01 (AB system, 2H, $\Delta v = 42$ Hz, $\delta_A = 1.06$ (d, 1H, $J_{AB} = 15.0$ Hz), $\delta_B = 0.96$ (d, 1H, $J_{AB} = 15.0$ Hz)), 1.10 (d, 3H, $J = 6.4$ Hz), 1.17 (AB system, 2H, $\Delta v = 73$ Hz, $\delta_A = 1.26$ (d, 1H, $J_{AB} = 14.3$ Hz), $\delta_B = 1.08$ (d, 1H, $J_{AB} = 14.3$ Hz)), 1.47 (AB part of ABX system, 2H, $\Delta v = 24$ Hz, $\delta_A = 1.50$ (dd, $J_{AB} = 14.3$ Hz, $J_{AX} = 2.6$ Hz), $\delta_B = 1.44$ (dd, $J_{AB} = 14.3$ Hz, $J_{BX} = 10.9$ Hz)), 3.15 (X part of ABX system, m, 1H); ^{13}C NMR δ (ppm) 0.6, 1.0, 28.1 (CH_3), 32.8, 35.0 (CH_2), 45.2 (CH), 50.9 (CH_2), 75.7 (C); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{31}NOSi_2 + H$: 262.2022. Found: 262.2031 ($M+H^+$).

4.4.2. (4*S*)-4-Amino-1-trimethylsilyl-2-trimethylsilylmethylheptan-2-ol 10b. Liquid purified by distillation on Kugelrohr: 187 °C/0.5 mmHg; yield: 80%; TLC: $R_f = 0.33$ (AcOEt)); $[\alpha]_D^{25} = -3$ (*c* 1.11, $CHCl_3$); IR (CCl_4): *v* (cm^{-1}) 3300; ^1H NMR δ 0.04 (s, 9H), 0.06 (s, 9H), 0.92 (t, 3H, $J = 6.8$ Hz), 1.02 (AB system, 2H, $\Delta v = 41$ Hz, $\delta_A = 1.07$ (d, 1H, $J_{AB} = 14.7$ Hz), $\delta_B = 0.97$ (d, 1H, $J_{AB} = 14.7$ Hz)), 1.15 (AB system, 2H, $\Delta v = 83$ Hz, $\delta_A = 1.26$ (d, 1H, $J_{AB} = 14.7$ Hz), $\delta_B = 1.05$ (d, 1H, $J_{AB} = 14.7$ Hz)), 1.18–1.46 (m, 5H), 1.50 (dd, 1H, $J = 14.1$ Hz, $J = 2.8$ Hz), 2.96 (m, 1H); ^{13}C NMR δ 1.0, 1.3, 14.2 (CH_3), 18.7, 32.4, 35.1, 43.9, 49.2 (CH_2), 49.4 (CH), 75.6 (C); MS (CI, methane) *m*/*z* calcd for $C_{14}H_{35}NOSi_2 + H$: 290 ($M+H^+$). Anal. Calcd for $C_{14}H_{35}NOSi_2$: C, 58.06; H, 12.18; N, 4.84. Found: C, 57.99; H, 13.52; N, 5.04.

4.4.3. (4*S*)-4-Amino-1-trimethylsilyl-2-trimethylsilylmethyltridecan-2-ol 10c. Oil; yield: 89%; TLC: $R_f = 0.25$ (AcOEt); ee = 80%; $[\alpha]_D^{25} = -2.5$ (*c* 1.07, $CHCl_3$); IR (CCl_4): *v* (cm^{-1}) 3300; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.00 (s, 9H), 0.02 (s, 9H), 0.83 (t, 3H, $J = 6.8$ Hz), 0.98 (AB system, 2H, $\Delta v = 34$ Hz, $\delta_A = 1.03$ (d, 1H, $J_{AB} = 14.4$ Hz), $\delta_B = 0.94$ (d, 1H, $J_{AB} = 14.4$ Hz)), 0.99 (d, 1H, $J = 14.3$ Hz), 1.18–1.27 (m, 15H), 1.29–1.36 (m, 2H), 1.44 (AB part of ABX system, 2H, $v = 21$ Hz, $\delta_A = 1.47$ (dd, 1H, $J_{AB} = 14.2$ Hz, $J_{AX} = 2.2$ Hz), $\delta_B = 1.41$ (dd, 1H, $J_{AB} = 14.2$ Hz, $J_{BX} = 11.5$ Hz)), 2.91 (partie X de système ABX, m, 1H), 3.21 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 0.8, 1.0, 14.8 (CH_3), 22.8, 25.7, 29.4, 29.6, 29.7, 32.0, 32.4, 35.2, 41.0, 49.3 (CH_2), 49.5 (CH), 75.8 (C); HRMS (EI) *m*/*z* calcd for $C_{20}H_{47}NOSi_2$–CH_2SiMe_3: 286.2566. Found: 286.2554 ($M-CH_2SiMe_3^+$).

4.5. (2*R*)-4-Trimethylsilylmethylpent-4-en-2-amine 5a

A solution of HCl 1 M (4.4 equiv) was added slowly to a cooled (0 °C) 0.5 M solution of (*R*)-**10a** in diethylether and stirred at 0 °C for 1 h. The excess of acid was neutralized with a saturated solution of sodium hydrogenocarbonate and the aqueous phase was extracted with ether. The organic phase was dried (K_2CO_3) and concentrated under atmospheric pressure. Liquid; yield: 93%; TLC: $R_f = 0.07$ (AcOEt); ee = 82%; $[\alpha]_D^{25} = +20$ (*c* 0.88, $CHCl_3$); Bp = 43 °C (1 mmHg); IR (CCl_4): *v* (cm^{-1}) 3080, 1630; ^1H NMR δ 0.00 (s, 9H), 1.07 (d,

3H, $J = 6.4$ Hz), 1.35 (br s, 2H), 1.51 (AB system, 2H, $\Delta\nu = 13$ Hz, $\delta_A = 1.52$ (d, 1H, $J_{AB} = 13.4$ Hz), $\delta_B = 1.49$ (d, 1H, $J_{AB} = 13.4$ Hz)), 1.94 (AB part of ABX system ABX, 2H, $\Delta\nu = 70$ Hz, $\delta_A = 2.03$ (dd, 1H, $J_{AB} = 13.6$ Hz, $J_{AX} = 4.6$ Hz), $\delta_B = 1.86$ (dd, 1H, $J_{AB} = 13.6$ Hz, $J_{BX} = 8.8$ Hz)), 3.05 (m, 1H), 4.60 (s, 1H), 4.62 (s, 1H); ^{13}C NMR δ −1.3, 23.9 (CH_3), 26.5 (CH_2), 44.6 (CH), 49.4, 109.6 (CH_2), 145.3 (C); HRMS (ESI) *m/z* calcd for $C_9H_{21}NSi + H$: 172.1521. Found: 172.1518 ($M+H^+$).

4.6. General procedure for preparation of 4-methylenepiperidines

4.6.1. From aminoallylsilane (*R*)-5a. To a solution of the aminoallylsilane (*R*)-**5a** in a mixture of THF and water (1:1 v/v; 0.73 mol L^{-1}) was added at ambient temperature aldehyde or cyclohexanone (1.2 equiv). The solution was stirred for 20 min and trifluoroacetic acid (1.1 equiv) was added dropwise. After stirring for one day, the reaction mixture was neutralized with a saturated solution of sodium hydrogenocarbonate and the aqueous phase was extracted with ether. The organic layers were collected, dried (K_2CO_3) and evaporated at atmospheric pressure. The crude product was purified by flash chromatography (elution gradient: pentane then pentane/diethylether).

4.6.2. From β-aminohydroxysilanes (*R*)-10a, (*S*)-10b and (*S*)-10c. To a solution of aminoalcohol (*S*)-**10b** and (*S*)-**10c** in a mixture of THF and water (1:1; 0.76 mol L^{-1}) was added at room temperature the carbonyl compound. The solution was stirred for 24 h and trifluoroacetic acid (10 equiv) added. One day after the addition, the acid was neutralized with a saturated solution of sodium hydrogenocarbonate. The aqueous phase was extracted with diethyl ether. The organic layers were collected, dried over K_2CO_3 and evaporated at atmospheric pressure. The crude product was purified by flash chromatography (elution gradient: pentane then pentane/diethyl ether).

4.6.3. (2*R*,6*S*)-2-Methyl-4-methylen-6-propylpiperidine 17a. Liquid. (a) *From aminoallylsilane* (*R*)-**5a**. Yield: 49%; TLC: $R_f = 0.38$ (AcOEt + drops of NH_4OH 28%); $[\alpha]_D^{21} = -4$ (*c* 1.05, $CHCl_3$); FTIR (film): ν (cm^{-1}) 3071, 1651; ^{1}H NMR δ 0.87 (t, 3H, $J = 7.0$ Hz), 1.06 (d, 3H, $J = 6.2$ Hz), 1.26–1.39 (m, 4H), 1.53 (br s, 1H), 1.67 (t, 1H, $J = 13.4$ Hz), 1.70 (t, 1H, $J = 13.4$ Hz), 2.15 (d, 1H, $J = 13.4$ Hz), 2.20 (d, 1H, $J = 13.4$ Hz), 2.42–2.50 (m, 1H), 2.52–2.62 (m, 1H), 4.59 (s, 2H); ^{13}C NMR δ 14.2 (CH_3), 19.1 (CH_2), 22.7 (CH_3), 39.3, 41.3, 43.4 (CH_2), 52.3, 57.5 (CH), 107.6 (CH_2), 146.9 (C); HRMS (ESI) *m/z* calcd for $C_{10}H_{19}N + H$: 154.1596. Found: 154.1591 ($M+H^+$). (b) *From aminohydroxysilane* (*R*)-**10a**. Yield: 53%; $[\alpha]_D^{21} = -5.5$ (*c* 0.94, $CHCl_3$). (c) *From aminohydroxysilane* (*S*)-**10b**. Yield: 34%; $[\alpha]_D^{21} = -5.5$ (*c* 0.93, $CHCl_3$).

4.6.4. (2*R*,6*R*)-2-Methyl-4-methylen-6-propenylpiperidine 18a. *From aminoallylsilane* (*R*)-**5a**. Liquid, yield: 39%; TLC: $R_f = 0.56$ (AcOEt + drops of NH_4OH 28%); $[\alpha]_D^{21} = -4$ (*c* 0.86, $CHCl_3$); ee = 78%; FTIR (film): ν (cm^{-1}) 3071, 1651; ^{1}H NMR δ 1.08 (d, 3H, $J = 6.2$ Hz), 1.63 (d, 3H, $J = 6.3$ Hz), 1.72 (t, 1H, $J = 12.5$ Hz), 1.86 (t, 1H, $J = 12.2$ Hz), 2.13–2.17 (2H, m), 2.58–2.66 (m, 1H), 3.01 (ddd, 1H, $J = 11.3$ Hz, $J = 6.9$ Hz, $J = 2.6$ Hz), 4.63 (2H, s), 5.43 (ddd, 1H, $J = 15.3$ Hz, $J = 6.9$ Hz, $J = 1.4$ Hz), 5.58 (dq, 1H, $J = 6.3$ Hz, $J = 15.3$ Hz); ^{13}C NMR δ 17.8, 22.6 (CH_3), 41.3, 42.9 (CH_2), 53.0, 60.1 (CH), 108.0 (CH_2), 125.8, 134.1 (CH), 146.3 (C); HRMS (ESI) *m/z* calcd for $C_{10}H_{17}N + H$: 152.1439. Found: 152.1457 ($M+H^+$).

4.6.5. (2*R*,6*S*)-2-Methyl-4-methylen-6-nonylpiperidine 19a. Liquid. (a) *From aminoallylsilane* (*R*)-**5a**. Yield: 49%; TLC: $R_f = 0.44$ (AcOEt + drops of NH_4OH 28%); $[\alpha]_D^{21} = -1.5$ (*c* 0.94, $CHCl_3$); ee = 28% FTIR (film): ν (cm^{-1}) 3071, 1651; ^{1}H NMR δ 0.83 (t, 3H, $J = 7.0$ Hz), 1.07 (d, 3H, $J = 6.2$ Hz), 1.14–1.46 (m, 16H), 1.67 (t, 1H, $J = 12.8$ Hz), 1.70 (t, 1H, $J = 12.8$ Hz), 2.16 (d, 1H, $J = 13.2$ Hz), 2.19 (d, 1H, $J = 13.2$ Hz), 2.41–2.49 (m, 1H), 2.53–2.62 (m, 1H), 4.59 (s, 2H); ^{13}C NMR δ 14.1 (CH_3), 22.8 (CH_3), 22.7, 26.0, 29.3, 29.6, 29.7, 29.8, 31.9, 37.2, 41.3, 43.5 (CH_2), 53.3, 57.9 (CH), 107.6 (CH_2), 146.9 (C); HRMS (EI) *m/z* calcd for $C_{16}H_{31}N - CH_3$: 222.2222. Found: 222.2200 ($M-CH_3^+$). (b) *From aminoalcohol* (*R*)-**10a**. Yield: 73%; $[\alpha]_D^{21} = -4.5$ (*c* 0.98, $CHCl_3$); ee = 74%. (c) *From aminohydroxysilane* (*S*)-**10c**. Yield: 53%; $[\alpha]_D^{21} = -6$ (*c* 1.00, $CHCl_3$); ee = 76% (method A).

4.6.6. (2*R*,6*S*)-2-Methyl-4-methylen-6-undecylpiperidine 20a. Liquid (**a**) *From aminoallylsilane* (*R*)-**5a**. Yield: 58%; TLC: $R_f = 0.56$ (AcOEt + drops of NH_4OH 28%); $[\alpha]_D^{21} = -2.5$ (*c* 1.16, $CHCl_3$); ee = 38%; FTIR (film): ν (cm^{-1}) 3071, 1651; ^{1}H NMR δ 0.86 (t, 3H, $J = 6.6$ Hz), 1.09 (d, 3H, $J = 6.2$ Hz), 1.20–1.43 (m, 20H), 1.70 (t, 1H, $J = 13.2$ Hz), 1.74 (t, 1H, $J = 13.2$ Hz), 2.19 (d, 1H, $J = 12.7$ Hz), 2.22 (d, 1H, $J = 12.7$ Hz), 2.43–2.51 (m, 1H), 2.55–2.65 (m, 1H), 4.62 (s, 2H); ^{13}C NMR δ 14.1, 22.7 (CH_3), 22.8, 26.0, 29.4, 29.6, 29.7, 29.8, 31.9, 37.2, 41.4, 43.5 (CH_2), 53.3, 57.9 (CH), 107.6 (CH_2), 147.0 (C); HRMS (EI) *m/z* calcd for $C_{18}H_{35}N$: 265.2769. Found: 265.2765 (M^+). (b) *From aminohydroxysilane* (*R*)-**10a**. Yield: 70%; ee = 64%.

4.6.7. (2*R*,6*R*)-2-Methyl-4-methylen-6-phenylpiperidine 21a. Liquid (**a**) *From aminoallylsilane* (*R*)-**5a**. Yield: 70%; TLC: $R_f = 0.85$ (AcOEt + drops of NH_4OH 28%); $[\alpha]_D^{21} = -9.5$ (*c* 1.12, $CHCl_3$); ee = 74%; FTIR (film): ν (cm^{-1}) 3071, 1651; ^{1}H NMR δ 1.12 (d, 3H, $J = 6.4$ Hz), 1.60 (br s, 1H), 1.85 (t, 1H, $J = 12.9$ Hz), 2.14 (t, 1H, $J = 12.8$ Hz), 2.22 (1H, d, $J = 12.8$ Hz), 2.32 (1H, d, $J = 12.8$ Hz), 2.70–2.77 (m, 1H), 3.59 (dd, 1H, $J = 2.7$ Hz, $J = 11.4$ Hz), 4.67–4.69 (2H, m), 7.20–7.35 (m, 5H); ^{13}C NMR δ 22.7 (CH_3), 42.9, 43.3 (CH_2), 53.7, 62.9 (CH), 108.2 (CH_2), 126.7, 127.2, 128.4 (CH), 144.5. 146.7 (C); HRMS (EI) *m/z* calcd for $C_{13}H_{17}N$: 187.1361. Found: 187.1370 (M^+). (b) *From aminohydroxysilane* (*R*)-**10a**. Yield: 70%; $[\alpha]_D^{21} = -11.5$ (*c* 1.09, $CHCl_3$); ee = 84%.

4.6.8. (2*R*)-Methyl-4-methylen-1-aza-spiro[5,5]undecane 22. Liquid (a) *From aminoallylsilane* (*R*)-**5a**. Yield:

46%; TLC: $R_f = 0.55$ (AcOEt + drops of NH_4OH 28%); $[\alpha]_D^{21} = 0$ (*c* 1.04, $CHCl_3$); ee = 24%; FTIR (film): *v* (cm^{-1}) 3071, 1651; ^1H NMR δ 1.03 (d, 3H, $J = 6.2$ Hz), 1.28–1.55 (m, 11H), 1.65 (t, 1H, $J = 10.7$ Hz), 1.77 (d, 1H, $J = 12.7$ Hz), 2.15–2.23 (2H, m), 2.80–2.88 (m, 1H), 4.56–4.58 (m, 1H), 4.66–4.68 (m, 1H); ^{13}C NMR δ 21.8, 21.9, 31.7, 40.9 (CH_2), 23.1 (CH_3), 43.9, 44.8 (CH_2), 46.1 (CH), 52.9 (C), 108.8 (CH_2), 145.1 (C); HRMS (EI) *m/z* calcd for $C_{12}H_{21}N$: 179.1674. Found: 179.1667 (M^+). (b) *From aminohydroxysilane* (*R*)-**10a**. Yield: 25%; $[\alpha]_D^{21} = 0$ (*c* 0.98, $CHCl_3$); ee = 14%.

4.7. General procedure for preparation of 24

To a solution of aminohydroxysilane (*R*)-**10a** in a mixture of THF and water (1:1; 0.76 mol L^{-1}) was added at room temperature the carbonyl compound. The mixture was stirred 24 h and extracted with diethyl ether. The organic layers were collected, dried over K_2CO_3 and concentrated. The crude product was purified by flash chromatography (elution gradient: cyclohexane then cyclohexane/AcOEt).

4.7.1. (4*R*)-4-Methyl-2-nonyl-6,6-bis-trimethylsilyl-methyl-[1,3]-oxazinane 24a. Oil; yield: 79%; TLC: $R_f = 0.64$ (AcOEt/cyclohexane 1:9); $[\alpha]_D^{25} = +17.5$ (*c* 1.08, $CHCl_3$); ee = 82%; ^1H NMR δ 0.05 (s, 9H), 0.06 (s, 9H), 0.88 (t, 3H, $J = 6.8$ Hz), 0.93 (d, 1H, $J = 11.2$ Hz), 1.04 (d, 3H, $J = 6.4$ Hz), 1.07–1.51 (m, 21H); 2.88–2.97 (m, 1H), 4.26 (t, 1H, $J = 5.2$ Hz); ^{13}C NMR δ 0.8, 1.2, 14.2, 22.8 (–CH_3), 22.7, 25.1, 26.4, 29.4, 29.6, 29.8, 32.0, 35.0, 36.7 (CH_2), 46.2 (CH), 47.3 (CH_2), 76.7 (C), 80.8 (CH); MS (ESI) *m/z* for $C_{22}H_{49}NOSi_2$: 400 ($M+H^+$).

4.7.2. (4*R*)-4-Methyl-2-phenyl-6,6-bis-trimethylsilyl-methyl-[1,3]-oxazinane 24b. Oil; yield: 59%; TLC: $R_f = 0.70$ (AcOEt/cyclohexane 2:8); $[\alpha]_D^{25} = -5$ (*c* 0.91, $CHCl_3$); ee = 82%; ^1H NMR δ 0.00 (s, 9H), 0.04 (s, 9H), 1.01 (d, 1H, $J = 14.7$ Hz), 1.05 (d, 3H, $J = 6.4$ Hz), 1.15–1.24 (m, 3H), 1.37 (d, 1H, $J = 14.8$ Hz), 1.51 (dd, 1H, $J = 2.9$ Hz, $J = 13.2$ Hz), 5.27 (s, 1H), 7.19–7.46 (m, 5H); ^{13}C NMR δ 0.9, 1.2, 22.7 (–*C*H_3), 26.3, 35.0 (CH_2), 46.6 (CH), 47.2 (CH_2), 77.8 (C), 82.3 (CH), 126.3, 128.1, 128.8 (CH), 141.5 (C); MS (ESI) *m/z* for $C_{19}H_{34}NOSi_2$: 350 ($M+H^+$).

4.8. General procedure for oxidation of 4-methylenepiperidines 19a and 19b

To a solution of 4-methylenepiperidine **19a** or **19b** prepared from aminohydroxysilane (*R*)-**10a** (2.3–2.5 mmol) in aqueous acetic acid solution (80%, 0.09 mol L^{-1}) was added sodium paraperiodate ($Na_3H_3IO_6$, 2.2 equiv) and a crystal of osmium tetroxide. The mixture was stirred for 22 h at 10 °C and acetic acid then evaporated under vacuum. A saturated solution of sodium hydrogenocarbonate was added and the aqueous phase extracted with dichloromethane. The organic layers were collected, dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography (elution gradient: AcOEt/cyclohexane, 25:75–1:1).

4.8.1. (2*R*,6*S*)-2-Methyl-6-nonylpiperidin-4-one 25. White solid; yield: 68%; TLC: $R_f = 0.51$ (AcOEt + drops of NH_4OH 28%); $[\alpha]_D^{25} = -1$ (*c* 0.79, $CHCl_3$) {lit.[13b] $[\alpha]_D^{25} = -1.1$ (*c* 1.56, $CHCl_3$)}; mp = 25–28 °C (lit.[13b] mp = 29–30 °C); FTIR (KBr): *v* (cm^{-1}) 1720; ^1H NMR δ 0.83 (t, 3H, $J = 6.8$ Hz), 1.19 (d, 3H, $J = 6.2$ Hz), 1.23–1.56 (m, 17H), 2.01–2.11 (m, 2H), 2.32–2.41 (m, 2H), 2.81–2.87 (m, 1H), 2.93–3.01 (m, 1H); ^{13}C NMR δ 14.2, 22.7 (CH_3), 22.7, 25.8, 29.4, 29.6, 29.7, 31.9, 37.1, 48.2, 50.2 (CH_2), 52.2, 56.7 (CH), 210.0 (C); MS (EI) *m/z* for $C_{15}H_{29}NO$: 239 (M^+).

4.8.2. (2*R*,6*S*)-2-Methyl-6-undecylpiperidin-4-one 27. White solid; yield: 67%; TLC: $R_f = 0.55$ (AcOEt + drops of NH_4OH 28%); $[\alpha]_D^{25} = -1.5$ (*c* 0.89, $CHCl_3$); mp = 38–40 °C; FTIR (KBr): *v* (cm^{-1}) 1720; ^1H NMR δ 0.87 (t, 3H, $J = 6.8$ Hz), 1.21 (d, 3H, $J = 6.4$ Hz), 1.22–1.56 (m, 20H), 2.01–2.12 (m, 2H), 2.17 (br s, 1H), 2.30–2.39 (m, 2H), 2.79–2.87 (m, 1H), 2.92–3.01 (m, 1H); ^{13}C NMR δ 14.2, 22.6 (CH_3), 22.7, 25.7, 29.5, 29.5, 29.6, 31.9, 37.0, 48.1, 50.1 (CH_2), 52.2, 56.6 (CH), 209.5 (C); MS (EI) *m/z* for $C_{17}H_{33}NO$: 267 (M^+).

4.9. (2*R*,4*S*,6*S*)-2-Methyl-6-nonylpiperidin-4-ol, (+)-alkaloid 241D 4

To a solution of piperidin-4-one **25** (0.15 g, 0.63 mmol) in methanol (3.7 mL) was added sodium borohydride (0.04 g, 1.08 mmol, 1.7 equiv). The mixture was stirred for 10 min and a saturated solution of ammonium chloride added. The aqueous phase was extracted with dichloromethane. The organic layers were collected, dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography (elution gradient: AcOEt then AcOEt/methanol 9:1) to give 0.10 g of **4**. White solid; yield: 66%; TLC: $R_f = 0.33$ (AcOEt + drops of NH_4OH 28%); $[\alpha]_D^{25} = +5.5$ (*c* 1.04, MeOH) {lit.[13a] $[\alpha]_D^{25} = +6.5$ (*c* 2, MeOH)}; ee = 74%; mp = 106 °C (lit.[13a] mp = 108–109 °C); spectral data are identical to literature;[13a] MS (ESI) *m/z* for $C_{15}H_{31}NO + H$: 242 ($M+H^+$).

4.10. (7*R*,9*S*)-7-Methyl-9-undecyl-1,4-dithia-8-aza-spiro[4.5]decane 28

To a solution of piperidin-4-one **27** (0.20 g, 0.75 mmol) in dry dichloromethane (1.25 mL) was added ethanedithiol (0.71 g, 7.5 mmol, 10 equiv) and boron trifluoride etherate (0.24 mL, 1.89 mmol, 2.5 equiv). The mixture was stirred for 20 h and hydrolyzed with a solution of sodium hydroxide 1 M. The aqueous phase was extracted with dichloromethane. The organic layers were collected, washed with a solution of sodium hydroxide 1 M, dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography (AcOEt) to give 0.21 g of **28**. Liquid; yield: 82%; TLC: $R_f = 0.42$ (AcOEt); $[\alpha]_D^{25} = +6$ (*c* 0.80, $CHCl_3$) {lit.[14c] $[\alpha]_D^{25} = +7.36$ (*c* 1.3, $CHCl_3$)}; spectral data are identical to literature;[14c] MS (EI) *m/z* for $C_{19}H_{37}NS_2$: 343 (M^+).

4.11. (2*R*,6*S*)-2-Methyl-6-undecylpiperidine hydrochloride, (+)-isosolenopsin A hydrochloride 3a

To a solution of **28** (0.20 g, 0.58 mmol) in absolute ethanol (9.5 mL) was added Raney nickel (4.38 g). The mixture was placed under hydrogen atmosphere and heated to reflux for 5 h. After cooling, the reaction mixture was filtered on Vericel® membrane and washed with diethylether. The filtrate was concentrated and the crude product was diluted in diethylether (10 mL). To this solution was added a solution of hydrochloric acid 1 M in diethyl ether (1 mL). A solid precipitated and was then recrystallized in a mixture of ethanol and AcOEt (1:3). 0.07 g of (+)-isosolenopsin A hydrochloride was obtained. White needles; yield: 43%; $[\alpha]_D^{25} = +5.5$ (*c* 1.00, $CHCl_3$) {lit.[14c] $[\alpha]_D^{25} = +10$ (*c* 1.17, $CHCl_3$)}; ee = 64%; mp = 135–140 °C (lit.[14c] mp = 150–151 °C); spectral data are identical to literature;[14b] MS (ESI) *m/z* for $C_{17}H_{35}NCl - HCl + H$: 253 ($M+H-HCl^+$).

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