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A general and enantiodivergent method for the asymmetric synthesis of piperidine alkaloids: concise synthesis of (*R*)-pipecoline, (*S*)-coniine and other 2-alkylpiperidines

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Abstract—A simple and very efficient protocol for the preparation of highly enantioenriched 2-alkylpiperidines has been set up, which allows the preparation of the final heterocycles with any wanted configuration at the stereogenic center starting from the same starting material. The key step of the synthesis relies on a diastereodivergent aza-Michael reaction protocol using the readily available and cheap reagent (+)-(*S*,*S*)-pseudoephedrine as chiral auxiliary.

1. Introduction

The piperidine ring is an ubiquitous structural feature shared by many natural products and therapeutics. As a consequence, the development of short, versatile, and efficient procedures for their stereocontrolled preparation represents a very important field of research for the organic chemists.[1] In particular, simple 2-alkyl substituted piperidines play an important role as key targets for the pharmaceutical industry because they exhibit an extensive range of biological activities. For example, *pipecoline* and *coniine* (Fig. 1) are alkaloids found as constituents of the poisonous hemlock (*Conium Maculatum* L.) and have been considered as excellent targets for the demonstration of the performance achieved by the new methodologies developed for the asymmetric synthesis of piperidines.

As it can be seen in the two examples shown in Figure 1, it is very often found in naturally occuring 2-alkylpiperidines that the configuration of the stereogenic center present at the heterocycle moiety varies across the different members of this family of compounds. In this context, when planning the asymmetric synthesis of any member of this family using many of the already reported procedures, a careful election of the chiral starting material, auxiliary, ligand or catalyst employed in the generation of this stereocenter is necessary in order to prepare the final compound with the right configuration. This means that if one wants to employ a general and modular route for the synthesis of a wide number of 2-alkylpiperidines both enantiomers of this chiral starting material, auxiliary, ligand or catalyst have to be commercially available.

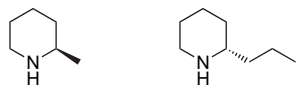

Figure 1. The structure of two relevant 2-alkylpiperidine alkaloids.

As a consequence, the design of enantiodivergent protocols, which allows the stereoselective preparation of a chiral compound in any wanted configuration using the same chirality source is a challenging task for the synthetic organic chemist. In this context, we have recently shown that the cheap and commercially available chiral aminoalcohol (+)-(*S*,*S*)-pseudoephedrine can play the role as an excellent chiral auxiliary in asymmetric aza-Michael reactions.[2] More interestingly, a simple modification of its structure, such as the derivatization of the OH group as a bulky trialkylsilyl ether, leads to the formation of the corresponding aza-Michael adduct with the opposite configuration at the newly created stereogenic center, if compared with the same reaction using the unmodified chiral auxiliary, therefore presenting a stereodivergent protocol for the asymmetric synthesis of β-amino carbonyl compounds (Scheme 1).[3]

Here we report the efforts made in order to synthesize chiral enantioenriched 2-alkylpiperidines by the transformation of

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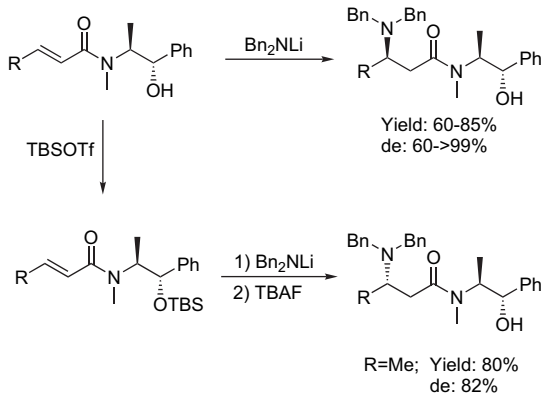
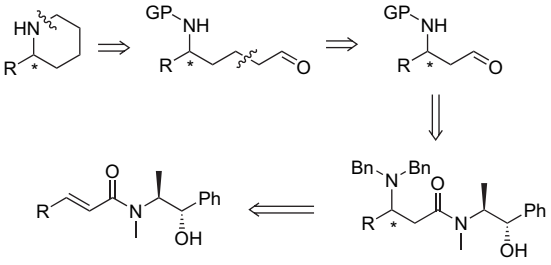


Scheme 1. Stereodivergent aza-Michael reaction using (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary.

the corresponding *N*-protected-β-amino amides derived from (+)-(*S*,*S*)-pseudoephedrine and prepared using our recently reported aza-Michael reaction protocol, following the retrosynthetic approach shown in Scheme 2.[4] The disconnection of the C6–N bond of the piperidine ring would lead to a δ-amino aldehyde structure, which could be obtained by a chain-elongation process from the corresponding, conveniently protected β-aminoaldehyde. This could be hypothetically prepared directly from a chiral nonracemic γ-amino alcohol, the latter being easily accessible from the already mentioned aza-Michael β-amino amide adducts. This strategy will allow us to synthesize two naturally occurring piperidine alkaloids such as (*R*)-pipecoline and (*S*)-coniine and other nonnatural derivatives. The preparation of these two natural alkaloids with opposite configuration will be approached in terms of the stereodivergent procedure shown in Scheme 1 and already optimized in our laboratories.[3]

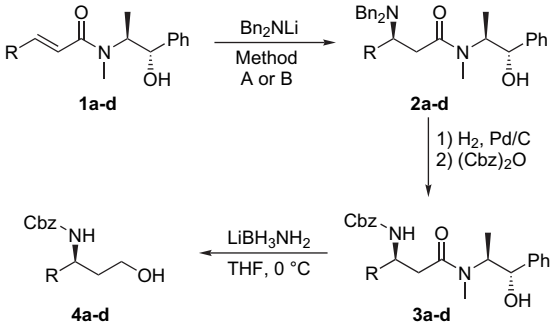


Scheme 2. Retrosynthetic plan for the enantiodivergent synthesis of 2-alkylpiperidines.

2. Results and discussion

2.1. Synthesis of (*R*)-2-alkylpiperidines[5]

We started our investigations with the preparation of enantioenriched chiral γ-amino alcohols **4a–d** starting from the corresponding (*S*,*S*)-(+)-pseudoephedrine derived enamides **1a–d** has been previously described by us (Scheme 3).[3] The employed protocol involved an aza-Michael reaction with lithium dibenzylamide as key step regarding the stereocontrolled installation of the stereogenic center. In this case, different experimental conditions had to be used depending upon the nature of the R alkyl chain introduced at the enamide precursor in order to reach to the highest possible yield and diastereoselectivity (Table 1). Next, we needed to carry out a protecting-group interconversion at the adducts **2a–d** in order to proceed to the removal of the chiral auxiliary by reduction, yielding cleanly the required γ-amino alcohols **4a–d**. We have already demonstrated that this protecting-group interconversion strategy was absolutely necessary in order to avoid epimerization at the stereogenic center during this reduction process.



Scheme 3. Asymmetric synthesis of γ-amino alcohols **4a–d**.

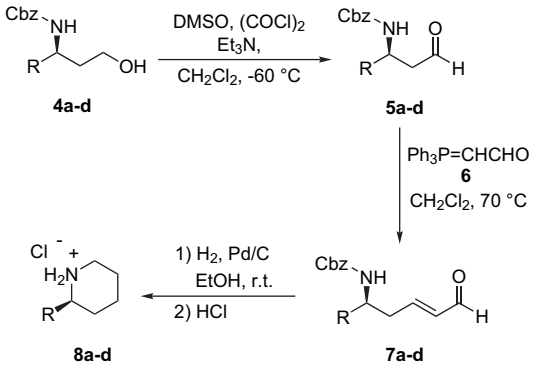
We next proceeded to carry out the oxidation of γ-amino alcohols **4a–d** under standard Swern-type conditions, isolating the corresponding β-amino aldehydes **5a–d** in good yields (Scheme 4, Table 2). This oxidation step proceeded in an extremely clean and smooth way, rendering directly the target compounds almost pure after work-up, which allowed us to use these β-amino aldehydes in the following transformation with no need of further purification. Nevertheless, as we also found that aldehydes **5a–d** showed an unexpected stability we proceeded to purify them by flash chromatography for better characterization process. The subsequent chain-elongation strategy was performed by a Wittig reaction

Table 1. Asymmetric synthesis of γ-amino alcohols **4a–d**

Entry	R	Prod.	Conditions[a]	Yield[b] %	dr[c]	Prod.	Yield[b] (%)	Prod.	Yield[b] (%)	ee[d] (%)
1	Me	**2a**	A	85	>99:1	**3a**	70	**4a**	85	98
2	Et	**2b**	B	88	94:6	**3b**	75	**4b**	76	88
3	*t*-Bu	**2c**	C	50	>99:1	**3c**	64	**4c**	72	98
4	Ph	**2d**	A	15	98:2	**3d**	43	**4d**	90[e]	98

[a] Method A: Bn_2NLi, toluene, −90 °C. Method B: Bn_2NLi/TMEDA (1:1), toluene, −90 °C. Method C: Bn_2NLi/CuI/TMEDA (2:1:2), THF, −90 °C.
[b] Yield of pure product after flash column chromatography purification.
[c] Determined by HPLC (Chiracel OD column, UV detector, hexanes/*iso*-propanol 95:5, flow rate: 1.00 mL/min).
[d] Determined by HPLC (Chiracel OJ column, UV detector, hexanes/*iso*-propanol 99:1, flow rate: 1.00 mL/min).
[e] Based on recovered **3d**.

with a suitable and commercially available phosphorous ylide reagent such as **6**, which allowed us to obtain the corresponding conjugated δ-amino aldehydes **7a–d** in moderate to good yields after flash column chromatography purification (Scheme 4, Table 2). The Wittig olefination proceeded with very high diastereoselectivity providing the expected *E* isomers in very high purity (^{1}H NMR analysis).



Scheme 4. Asymmetric synthesis of (*R*)-2-alkylpiperidines **8a–d**.

Table 2. Asymmetric synthesis of 2-alkylpiperidine hydrochlorides **8a–d**

Entry	R	Prod.	Yield[a] (%)	Prod.	Yield[a] (%)	Prod.	Yield (%)
1	Me	**5a**	79	**7a**	71	**8a**	84
2	Et	**5b**	62	**7b**	56	**8b**	78
3	*t*-Bu	**5c**	66	**7c**	37	**8c**	99
4	Ph	**5d**	77	**7d**	84	**8d**	91

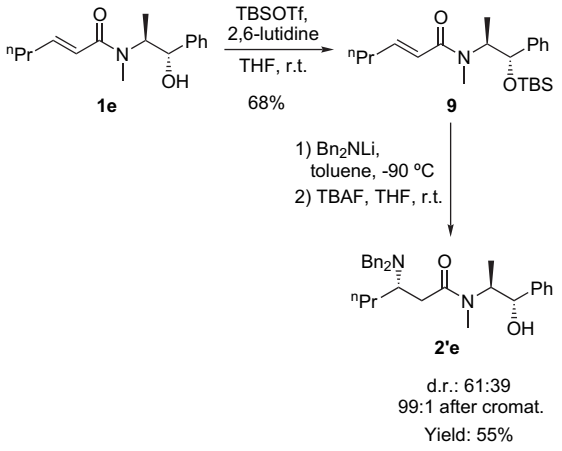
[a] Yield of pure product after flash column chromatography purification.

Indeed, these δ-amino aldehydes **7a–d** represent very suitable precursors of the desired piperidinic structures via a cascade process involving hydrogenation of the C=C double bond, followed by removal of the *N*-Cbz protecting group and a final intramolecular reductive amination step.[6] Therefore, derivatives **7a–d** were treated with H_2 in the presence of 10% Pd/C, yielding cleanly the final heterocycles in excellent yield. In order to easily handle these compounds, in particular those of high volatility, the crude reaction mixture was treated with concentrated HCl and hence, the corresponding piperidine hydrochlorides **8a–d** were isolated after crystallization (Scheme 4).

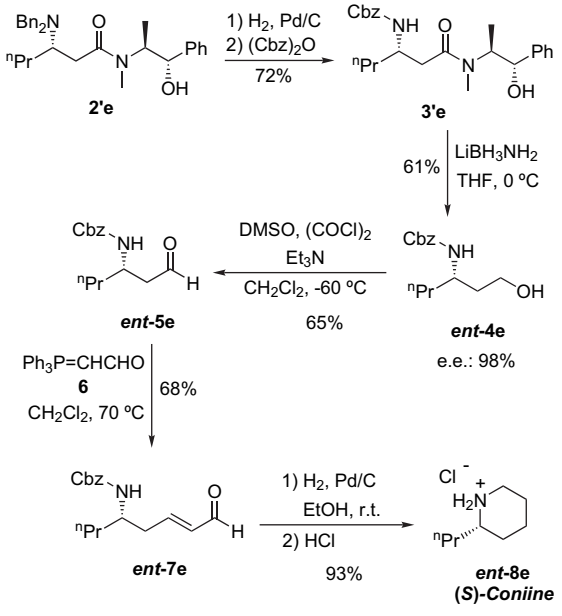
It has to be mentioned that hydrochloride **8a**, a derivative of the naturally occurring alkaloid (*R*)-pipecoline, was obtained in a 47% overall yield from the corresponding alcohol **4a** and in 29% yield from the corresponding aza-Michael adduct **2a**. The recorded data for the specific rotation value of compound **7a** matched with the reported data for natural (*R*)-pipecoline hydrochloride[7] and the same applies to the other nonnatural piperidines prepared by this synthetic pathway.[8]

2.2. Synthesis of (*S*)-coniine

As it was previously mentioned, the aza-Michael reaction of lithium dibenzylamide with *O*-TBS-protected enamides derived from (+)-(*S*,*S*)-pseudoephedrine has been exploited in our group for the preparation of β-amino amide adducts presenting opposite configuration at the newly created stereogenic center (Scheme 1). With this precedent in mind enamide **1e**, in which an *n*-Pr substituent was conveniently placed at the β-carbon of the conjugate acceptor was chosen as an appropriate precursor to the target alkaloid (*S*)-coniine. The preparation of substrate **9** was carried out by standard *O*-silylation of the corresponding (*S*,*S*)-pseudoephedrine enamide **1e** with TBSOTf (Scheme 5). The aza-Michael reaction of lithium dibenzylamide with enamide **9** yielded the corresponding β-amino amide **2′e** after removal of the TBS group by treatment of the crude reaction mixture with TBAF. HPLC analysis showed that the obtained major diastereomer corresponded to **2′e** with the opposite configuration at C3 with respect to that found in adducts **2a–d**, which was in good agreement with our previously reported diastereodivergent approach. Fortunately, and despite the moderate diastereoselectivity obtained in this aza-Michael reaction, compound **2′e** could be isolated in 98% de by flash column



Scheme 5.



Scheme 6. Asymmetric synthesis of (*S*)-coniine.

chromatography affording the necessary diastereomerically enriched material required in order to synthesize the desired piperidine alkaloid.

Next, debenzylation followed by treatment with dibenzyldicarbonate afforded the *N*-protected β-amino amide **3′e** in good yield and with no isomerization at C3 (Scheme 6). The LAB-mediated reduction of **3′e** led to the corresponding γ-amino alcohol ***ent*-4e** in good yield and with no loss of optical purity as confirmed by chiral HPLC. Subsequently, and following the strategy described before, alcohol ***ent*-4e** was oxidized to the corresponding β-amino aldehyde ***ent*-5e**, which was transformed into the corresponding α,β-unsaturated δ-amino aldehyde ***ent*-7e** after Wittig reaction with commercially available stabilized ylide **6**. The hydrogenation/deprotection/reductive amination sequence took place smoothly furnishing (*S*)-coniine hydrochloride ***ent*-8e** after acidic treatment. The obtained specific rotation value for a sample of ***ent*-8e** matched with that reported in the literature.[9]

3. Conclusions

To sum up, we have shown that our recently reported protocol for carrying out stereodivergent aza-Michael reactions using (+)-(*S*,*S*)-pseudoephedrine as chiral auxiliary can be a very reliable tool for the asymmetric synthesis of valuable chiral compounds such as 2-alkylpiperidines, including naturally occurring (*R*)-pipecoline and (*S*)-coniine. The synthetic route presented herein is very straightforward, employs simple transformations and furnishes the final heterocycles in very high optical purity. The most remarkable feature of this methodology is that the final compounds can be obtained with any desired configuration at their stereogenic center using in all cases the same chirality source for exerting the desired high degree of stereocontrol, with no need for the availability of both enantiomeric forms of the chiral auxiliary employed.

4. Experimental section

4.1. General

^{1}H NMR and ^{13}C NMR spectra were acquired in a Bruker AC-250 and AV-500. THF and toluene were distilled from sodium/benzophenone and CH_2Cl_2 from CaH_2. Melting points were measured using a Gallenkamp apparatus in open capillary tubes. Optical rotations were recorded in cells with 10 cm path length on a Perkin–Elmer 241 MC polarimeter. Flash column chromatography was performed using silica gel Merck-60, 230–400 mesh ATMS or 70–230 mesh ATMS. IR spectra were recorded in a Perkin–Elmer R-1600 FTIR and Mattson Satellite FTIR. The MS spectra were measured on electronic ionization conditions in a Hewlett Packard 5989B spectrometer. GC–MS analyses were performed in a Hewlett Packard 5890II spectrometer using a Hp-5 (5% phenylmethylpolysiloxane, 30 m×0.25 mm×0.25 μm) column. Enantiomeric and diastereomeric excesses were measured by HPLC in a Waters 600A chromatograph using a photodiode array UV detector and a chiral stationary phase (Chiralcel OJ and Chiralcel OD columns, 0.46×25 cm). The synthesis of alcohols **4a–d** was described previously.

4.2. Synthesis of (*R*)-2-alkylpiperidines

4.2.1. General procedure for the Swern oxidation of the γ-amino alcohols 4a–d. A solution of DMSO (5.20 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise over a solution of oxalyl chloride (2.60 mmol) in CH_2Cl_2 at −60 °C and the mixture was stirred for 15 min at this temperature. Then, a solution of the corresponding alcohol **4a–d** (1.30 mmol) in CH_2Cl_2 was added via cannula over the mixture at −60 °C and the reaction mixture was stirred for 30 min. Then Et_3N (13.00 mmol) was added to the mixture at −60 °C and the reaction mixture was stirred for 15 min at −60 °C and for 30 min at rt. The reaction was then quenched with water (20 mL). The mixture was extracted with CH_2Cl_2 (3×15 mL), and the combined organic fractions were collected, dried over Na_2SO_4, and filtered. The solvent removed in vacuo, affording the desired aldehydes **5a–d** after column chromatography purification (hexanes/AcOEt 8:2).

4.2.1.1. (+)-(3*R*)-3-Benzyloxycarbonylaminobutanal (5a). This compound was obtained following the general method from alcohol **4a** (0.30 g, 1.34 mmol), DMSO (0.58 mL, 5.36 mmol), oxalyl chloride (0.34 mL, 2.68 mmol), and Et_3N (1.40 mL, 13.40 mmol) in 79% yield (0.23 g, 1.06 mmol). Data for **5a**: yellowish solid; mp: 75–77 °C; $[\alpha]_D^{20}$ +16.9 (*c* 0.7, CH_2Cl_2); IR (film): 3324, 1700; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.19 (d, J=6.8 Hz, 3H), 2.55 (m, 2H), 4.16 (m, 1H), 5.04 (s, 2H), 5.15 (m, 1H), 7.30 (m, 5H), 9.68 (s, 1H); ^{13}C NMR (50 MHz): δ 20.7, 42.7, 50.0, 66.6, 128.0, 128.1, 128.4, 136.3, 155.5, 200.8; MS (EI): *m*/*z* 206 (4), 137 (9), 122 (5), 108 (3), 91 (100), 87 (3), 72 (13), 65 (3), 56 (43).

4.2.1.2. (+)-(3*R*)-3-Benzyloxycarbonylaminopentanal (5b). This compound was obtained following the general method from alcohol **4b** (0.27 g, 1.14 mmol), DMSO (0.49 mL, 4.56 mmol), oxalyl chloride (0.29 mL, 2.28 mmol), and Et_3N (1.20 mL, 11.40 mmol) in 62% yield (0.17 g, 0.71 mmol). Data for **5b**: colorless oil; $[\alpha]_D^{20}$ +23.4 (*c* 0.2, CH_2Cl_2); IR (film): 3333, 1717, 1700; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.91 (t, J=7.5 Hz, 3H), 1.54 (m, 2H), 2.55 (m, 2H), 3.99 (m, 1H), 5.05 (s, 2H), 5.25 (m, 1H), 7.31 (m, 5H), 9.69 (s, 1H); ^{13}C NMR (50 MHz): δ 12.2, 27.6, 48.2, 48.5, 66.6, 127.6, 127.8, 128.3, 136.2, 155.8, 201.1; MS (EI): *m*/*z* 206 (2), 137 (7), 122 (4), 101 (6), 91 (100), 79 (7), 65 (32), 57 (36).

4.2.1.3. (+)-(3*S*)-3-Benzyloxycarbonylamino-4,4-dimethylpentanal (5c). This compound was obtained following the general method from alcohol **4c** (0.21 g, 0.79 mmol), DMSO (0.34 mL, 3.16 mmol), oxalyl chloride (0.20 mL, 1.58 mmol), and Et_3N (0.80 mL, 7.90 mmol) in 66% yield (0.14 g, 0.52 mmol). Data for **5c**: colorless oil; $[\alpha]_D^{20}$ +45.2 (*c* 0.6, CH_2Cl_2); IR (film): 3326, 1708; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.85 (s, 9H), 2.26 (m, 1H), 2.55 (m, 1H), 4.03 (m, 1H), 5.02 (m, 2H), 5.24 (m, 1H), 7.26 (m, 5H), 9.64* (s, 1H), 9.65 (s, 1H); ^{13}C NMR (50 MHz): δ 25.9, 34.4, 44.6, 54.5, 66.4, 127.6, 127.8, 128.2, 136.2, 156.0, 201.5; MS (EI): *m*/*z* 221 (6), 178 (8), 132 (2), 108 (17), 91 (100), 79 (16), 65 (8), 57 (32).

4.2.1.4. (−)-(3*S*)-3-Benzyloxycarbonylamino-3-phenylpropanal (5d). This compound was obtained following the general method from alcohol **4d** (0.21 g, 0.74 mmol), DMSO (0.32 mL, 2.96 mmol), oxalyl chloride (0.19 mL, 1.48 mmol), and Et_3N (0.75 mL, 7.40 mmol) in 77% yield (0.16 g, 0.57 mmol). Data for **5d**: colorless oil; $[\alpha]_D^{20}$ −7.5 (*c* 0.4, CH_2Cl_2); IR (film): 3326, 1702; ^1H NMR (250 MHz, $CDCl_3$): δ 2.93 (m, 2H), 5.06 (m, 2H), 5.26 (m, 1H), 5.55 (m, 1H), 7.27 (m, 10H), 9.71 (s, 1H); ^{13}C NMR (50 MHz): δ 49.4, 50.4, 66.9, 126.2, 127.8, 128.0, 128.1, 128.5, 136.1, 140.5, 155.6, 200.0; MS (EI): *m*/*z* 193 (2), 149 (7), 137 (8), 134 (10), 122 (4), 108 (25), 91 (100), 65 (21), 57 (32).

4.2.2. General procedure for the Wittig reaction of aldehydes 5a–d with ylide 6. Triphenylphosphoranylidenacetaldehyde **6** (2.45 mmol) was added to a solution of the corresponding aldehyde **5a–d** (0.50 mmol) in CH_2Cl_2 (20 mL) and the mixture was stirred at reflux for 15 h. Then, the reaction was cooled to rt and quenched with saturated NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2 (3×15 mL), and the combined organic fractions were collected, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, affording the desired aldehydes **7a–d** after flash column chromatography purification (hexanes/AcOEt 7:3).

4.2.2.1. (5*R*,2*E*)-5-Benzyloxycarbonylaminohex-2-enal (7a). This compound was obtained following the general method from aldehyde **5a** (0.11 g, 0.49 mmol) and triphenylphosphoranylidenacetaldehyde **6** (0.79 g, 2.45 mmol) in 71% yield (86 mg, 0.35 mmol). Data for **7a**: colorless oil; IR (film): 3324, 1704; ^1H NMR (250 MHz, $CDCl_3$): δ 1.18 (d, *J*=6.7 Hz, 3H), 2.46 (m, 2H), 3.94 (m, 1H), 4.87 (m, 1H), 5.1 (s, 2H), 6.10 (dd, *J*=15.4, 7.9 Hz, 1H), 6.77 (m, 1H), 7.32 (m, 5H), 9.45 (d, *J*=7.9 Hz, 1H). ^{13}C NMR (50 MHz): δ 20.7, 40.1, 46.0, 66.6, 128.1, 128.5, 134.9, 136.3, 153.8, 155.6, 193.7; MS (EI): *m*/*z* 136 (15), 108 (52), 105 (12), 91 (100), 84 (56), 79 (18), 66 (12).

4.2.2.2. (5*R*,2*E*)-5-Benzyloxycarbonylaminohept-2-enal (7b). This compound was obtained following the general method from aldehyde **5b** (0.10 g, 0.43 mmol) and triphenylphosphoranylidenacetaldehyde **6** (0.71 g, 2.15 mmol) in 56% yield (62 mg, 0.24 mmol). Data for **7b**: colorless oil; IR (film): 3318, 1703; ^1H NMR (250 MHz, $CDCl_3$): δ 0.92 (t, *J*=7.1 Hz, 3H), 1.49 (m, 2H), 2.47 (m, 2H), 3.76 (m, 1H), 4.93 (d, *J*=8.3 Hz, 1H), 5.06 (s, 2H), 6.10 (dd, *J*=15.8, 7.9 Hz, 1H), 6.76 (m, 1H), 7.30 (m, 5H), 9.43 (d, *J*=7.9 Hz, 1H); ^{13}C NMR (50 MHz): δ 10.18, 27.7, 38.2, 51.6, 66.6, 127.9, 128.0, 128.4, 130.9, 136.3, 154.2, 156.0, 193.7; MS (EI): *m*/*z* 151 (15), 108 (100), 105 (6), 91 (52), 79 (17), 65 (18), 51 (12).

4.2.2.3. (5*S*,2*E*)-5-Benzyloxycarbonylamino-6,6-dimethylhept-2-enal (7c). This compound was obtained following the general method from aldehyde **5c** (0.11 g, 0.42 mmol) and triphenylphosphoranylidenacetaldehyde **6** (0.70 g, 2.10 mmol) in 37% yield (45 mg, 0.15 mmol). Data for **7c**: colorless oil; IR (film): 3316, 1703; ^1H NMR (250 MHz, $CDCl_3$): δ 0.94 (s, 9H), 2.20 (m, 1H), 2.65 (m, 1H), 3.67 (td, *J*=10.1, 2.4 Hz, 1H), 4.71* (s, 1H), 4.75* (s, 1H), 5.06 (dd, *J*=19.0, 12.3 Hz, 2H), 6.07* (d, *J*=7.9 Hz, 1H), 6.13* (d, *J*=7.9 Hz, 1H), 6.78 (m, 1H), 7.31 (m, 5H), 9.39* (s, 1H), 9.42* (s, 1H); ^{13}C NMR (50 MHz): δ 26.2, 34.3, 34.7, 58.9, 66.7, 127.9, 128.1, 130.4, 130.5, 134.6, 136.4, 155.6*, 156.4*, 193.8; MS (EI): *m*/*z* 179 (3), 136 (5), 108 (100), 105 (64), 91 (20), 81 (25), 58 (42).

4.2.2.4. (5*S*,2*E*)-5-Benzyloxycarbonylamino-5-phenylpent-2-enal (7d). This compound was obtained following the general method from aldehyde **5d** (0.10 g, 0.35 mmol) and triphenylphosphoranylidenacetaldehyde **6** (0.58 g, 1.75 mmol) in 84% yield (91 mg, 0.29 mmol). Data for **7d**: colorless oil; IR (film): 3313, 1710; ^1H NMR (250 MHz, $CDCl_3$): δ 2.88 (m, 2H), 5.03 (d, *J*=11.9 Hz, 1H), 5.12 (d, *J*=11.9 Hz, 2H), 5.29 (d, *J*=6.7 Hz, 1H), 6.12 (dd, *J*=15.4, 7.5 Hz, 1H), 6.68 (m, 1H), 7.28 (m, 10H), 9.40 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (50 MHz): δ 39.5, 54.1, 67.0, 126.2, 128.0, 128.1, 128.2, 128.5, 128.9, 135.1, 136.1, 153.0, 193.6; MS (EI): *m*/*z* 175 (34), 108 (100), 105 (25), 98 (37), 91 (23), 79 (11), 65 (20), 51 (6).

4.2.3. General procedure for the cascade hydrogenation/deprotection/intramolecular reductive amination sequence: synthesis of piperidines 8a–d. A catalytic amount of Pd/C (10 mol %) was added to a solution of the corresponding aldehyde **7a–d** (0.30 mmol) in EtOH (20 mL) and the mixture was stirred under a 65 psi pressure of H_2 for 15 h at rt. Then, the mixture was filtered and concentrated HCl (0.1 mL) was added to the solution and the mixture was stirred at rt for 1 h after which the solvent was removed in vacuo obtaining the corresponding 2-alkylpiperidine hydrochlorides **8a–d**.

4.2.3.1. (+)-(2*R*)-2-Methylpiperidine hydrochloride ((+)-pipecoline hydrochloride) (8a). This compound was obtained following the general method from aldehyde **7a** (70 mg, 0.28 mmol) in 84% yield (32 mg, 0.24 mmol). Data for **8a**: white solid; mp: 192–194 °C (Et_2O); $[\alpha]_D^{20}$ +3.9 (*c* 1.1, EtOH); lit.[7] +3.97 (*c* 1.0, EtOH); IR (film): 3358; ^1H NMR (250 MHz, $CDCl_3$): δ 1.43 (m, 4H), 1.78 (m, 5H), 2.78 (m, 1H), 3.05 (m, 1H), 3.61 (m, 1H), 9.08 (br s, 1H), 9.47 (br s, 1H); ^{13}C NMR (50 MHz): δ 19.3, 21.7, 22.3, 30.3, 44.4, 53.0; MS (EI): *m*/*z* 84 (100), 70 (4), 56 (12).

4.2.3.2. (−)-(2*R*)-2-Ethylpiperidine hydrochloride (8b). This compound was obtained following the general method from aldehyde **7b** (65 mg, 0.25 mmol) in 78% yield (29 mg, 0.19 mmol). Data for **8b**: white solid; mp: 205–206 °C (Et_2O); $[\alpha]_D^{20}$ −1.2 (*c* 0.2, EtOH); lit.[7] $[\alpha]_D^{20}$ −1.42 (*c* 0.2, EtOH). IR (film): 3356; ^1H NMR (250 MHz, $CDCl_3$): δ 0.98 (m, 3H), 1.28–2.05 (m, 8H), 2.82 (m, 2H), 3.39 (m, 1H), 9.07 (br s, 1H), 9.37 (br s, 1H); ^{13}C NMR (50 MHz): δ 9.8, 22.1, 22.3, 26.3, 27.5, 44.7, 58.5; MS (EI) *m*/*z* 98 (100), 84 (24), 71 (42), 67 (7), 56 (5).

4.2.3.3. (+)-(2*S*)-2-*tert*-Butylpiperidine hydrochloride (8c). This compound was obtained following the general method from aldehyde **7c** (62 mg, 0.22 mmol) in 99% yield (0.37 mg, 0.21 mmol). Data for **8c**: white solid; mp: 193–195 °C (Et_2O); $[\alpha]_D^{20}$ +2.1 (*c* 0.2, EtOH); IR (film): 3358; ^1H NMR (250 MHz, $CDCl_3$): δ 1.18 (s, 9H), 1.30–2.22 (m, 6H), 2.63 (m, 1H), 2.88 (m, 1H), 3.16 (m, 1H), 8.75 (br s, 2H); ^{13}C NMR (50 MHz): δ 22.0, 23.1, 24.1, 26.9, 33.3,

47.1, 67.2; MS (EI): *m*/*z* 126 (100), 113 (34), 95 (26), 83 (24), 61 (9).

4.2.3.4. (+)-(2*S*)-2-Phenylpiperidine hydrochloride (8d). This compound was obtained following the general method from aldehyde **7d** (55 mg, 0.18 mmol) in 91% yield (32 mg, 0.16 mmol). Data for **8d**: white solid; mp: 192–195 °C (Et_2O); $[\alpha]_D^{20}$ +3.0 (*c* 0.2, EtOH); lit.[8] $[\alpha]_D^{20}$ −3.1 (*c* 0.2, EtOH) for the *R* isomer; IR (film): 3360; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.50–2.16 (m, 6H), 2.76 (m, 1H), 3.08 (m, 1H), 3.90 (m, 1H), 7.32 (m, 3H), 7.58 (m, 2H), 9.49 (br s, 2H); ^{13}C NMR (50 MHz): δ 21.6, 23.1, 30.1, 45.7, 61.2, 127.0, 128.0, 128.5, 129.0, 129.1, 136.4; MS (EI) *m*/*z* 143 (10), 131 (7), 114 (23), 81 (7), 76 (100), 58 (8).

4.3. Asymmetric synthesis of (*S*)-coniine

4.3.1. (+)-(1′*S*,2′*S*,2*E*)-*N*-(2′-*tert*-Butyldimethylsilyloxy-1′-methylethyl-2′-phenyl)-*N*-methylhex-2-enamide (9). 2,6-Lutidine (1.25 mL, 10.72 mmol) was added to a solution of the amide **1e** (2.00 g, 7.66 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and then *tert*-butyldimethyilsilyl triflate (1.79 mL, 7.70 mmol) was added at once. Next, the reaction mixture was cooled to rt and stirred for 12 h after which it was quenched with saturated NH_4Cl (20 mL) and diluted with water (20 mL). The mixture was extracted with CH_2Cl_2 (3×15 mL), and the combined organic fractions were collected, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, affording the desired amide **9** after column chromatography purification (hexanes/AcOEt, 8:2) in 68% yield (1.96 g, 5.20 mmol). Data for **9**: colorless oil; $[\alpha]_D^{20}$ +66.8 (*c* 0.4, CH_2Cl_2); IR (film): 1654, 1617; ^{1}H NMR (250 MHz, $CDCl_3$) (3:1 rotamer ratio; * indicates minor rotamer resonances): δ −0.39 (s, 3H), −0.37* (s, 3H), −0.10 (s, 3H), −0.05* (s, 3H), 0.72 (s, 9H), 0.78* (s, 9H), 0.88 (m, 6H), 1.38 (m, 2H), 2.05 (m, 2H), 2.77* (s, 3H), 2.82 (s, 3H), 4.04 (m, 1H), 4.42 (d, *J*=7.5 Hz, 1H), 6.08* (d, *J*=15.1 Hz, 1H), 6.19 (d, *J*=15.1 Hz, 1H), 6.66 (m, 1H), 7.20 (m, 5H); ^{13}C NMR (50 MHz) (* indicates minor rotamer resonances): δ −5.6*, −5.0, −3.8, 13.2*, 13.4, 15.3, 16.5, 17.6, 21.3, 25.5, 27.4*, 34.3, 58.2, 75.8*, 76.6, 121.1*, 121.6, 126.6, 127.2, 128.1, 141.9, 144.2, 145.6*, 166.6*, 167.9; MS (EI): *m*/*z* 375 (M^+, 4), 261 (2), 243 (3), 166 (12), 115 (5), 70 (56), 58 (100). Anal. Calcd for $C_{22}H_{37}NO_2$: C, 70.35; H, 9.93; N, 3.73. Found: C, 70.27; H, 9.76; N, 4.37.

4.3.2. (+)-(1′*S*,2′*S*,3*S*)-3-Dibenzylamino-*N*-(2′-hydroxy-1′-methylethyl-2′-phenyl)-*N*-methylhexanamide (2′e). *n*-BuLi (4.24 mL of a 1.6 M solution in hexanes, 6.78 mmol) was added to a solution of dibenzylamine (1.37 mL, 6.92 mmol) in dry toluene (20 mL) at −78 °C and the mixture was stirred at −78 °C for 30 min. The mixture was cooled and added dropwise for 2 h over a solution of *O*-protected amide **9** (0.64 g, 1.71 mmol) in dry toluene (20 mL) at −90 °C. Then, the reaction mixture was stirred at −90 °C for 20 h after which it was quenched with saturated NH_4Cl (15 mL). The mixture was extracted with CH_2Cl_2 (3×25 mL), and the combined organic fractions were collected, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. THF (1 M) solution of TBAF (6.84 mL, 6.84 mmol) was added to a solution of this material in THF (20 mL) and this mixture was stirred at rt for 1 h. Then, the reaction was quenched with saturated NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2 (3×15 mL), and the combined organic fractions were collected, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, affording the desired amide **2′e** after column chromatography purification (hexanes/AcOEt 1:1) in 55% yield (0.53 g, 1.15 mmol). Data for **2′e**: colorless oil; $[\alpha]_D^{20}$ +29.4 (*c* 0.3, CH_2Cl_2); IR (film): 3378, 1615; ^{1}H NMR (250 MHz, $CDCl_3$) (3:1 rotamer ratio; * indicates minor rotamer resonances): δ 0.68* (d, *J*=6.5 Hz, 3H), 0.81 (m, 3H), 1.06 (d, *J*=6.5 Hz, 3H), 1.26 (m, 2H), 1.57 (m, 2H), 2.26 (m, 1H), 2.67 (m, 1H), 2.71 (s, 3H), 2.85* (s, 3H), 3.17 (m, 1H), 3.42 (m, 2H), 3.76 (m, 2H), 4.52 (m, 3H), 7.30 (m, 15H); ^{13}C NMR (50 MHz) (* indicates minor rotamer resonances): δ 14.0, 14.4*, 15.3, 19.9, 26.9, 32.9*, 33.7, 34.2*, 34.4, 53.2*, 53.5, 54.5*, 55.9, 58.2, 58.8, 75.3*, 76.5, 126.4, 126.7, 126.8, 126.9, 127.6, 128.1, 128.3, 128.6, 128.8, 139.9, 141.2*, 142.3, 173.7*, 174.6; MS (EI): *m*/*z* 460 (M^+, 3), 441 (5), 365 (11), 196 (25), 170 (15), 105 (6), 91 (100), 58 (15). Anal. Calcd for $C_{30}H_{38}N_2O_2$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.81; H, 8.67; N, 6.43.

4.3.3. (+)-(1′*S*,2′*S*,3*S*)-3-(Benzyloxycarbonylamino)-*N*-methyl-*N*-(2′-hydroxy-1′-methylethyl-2′-phenyl)-hexanamide (3′e). *N*,*N*-Dibenzyl-β-amino amide **2′e** (1.20 g, 2.61 mmol) was hydrogenated in EtOH under 65 psi H_2 and Pd/C 10% for 18 h, after which the solvent was removed in vacuo. The obtained slurry was dissolved in dioxane/H_20 (1:1, 20 mL), treated with NaOH (1 M) (2.61 g, 2.61 mmol), and dibenzylcarbonate (0.95 g, 3.92 mmol) at rt and stirred for 18 h. The mixture was quenched with saturated NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic fractions were collected, dried over Na_2SO_4, filtered, and the solvent removed in vacuo affording the wanted *N*-Cbz-β-amino amide **3′e** (0.78 g, 1.88 mmol) after flash column chromatography (AcOEt/hexanes 1:1) in 72% yield. Data for **3′e**: colorless oil; $[\alpha]_D^{20}$ +51.7 (*c* 0.5, CH_2Cl_2); IR (film): 3330, 1703, 1619; ^{1}H NMR (250 MHz, $CDCl_3$) (3:1 rotamer ratio; * indicates minor rotamer resonances): δ 0.89 (d, *J*=5.5 Hz, 3H), 0.98* (d, *J*=5.2 Hz, 3H), 1.32 (m, 4H), 2.43 (m, 1H), 2.54 (m, 1H), 2.77 (s, 3H), 2.83* (s, 3H), 3.94 (m, 1H), 4.41 (m, 2H), 5.03 (s, 2H), 5.79 (m, 1H), 7.30 (m, 10H); ^{13}C NMR (50 MHz) (* indicates minor rotamer resonances): δ 13.6, 13.9*, 15.3, 19.3, 26.6*, 32.0, 36.3, 37.7*, 38.1, 48.0, 48.4, 66.1, 74.9*, 75.5, 126.2, 126.6, 127.3, 127.6, 127.8, 128.0, 128.1, 128.2, 136.5, 141.5*, 142.0, 156.0, 171.8*, 172.3; MS (EI): *m*/*z* 396 (8), 320 (12), 291 (13), 278 (43), 171 (5), 149 (28), 107 (4), 91 (100), 58 (12). Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79. Found: C, 69.57; H, 7.67; N, 6.67.

4.3.4. (+)-(3*S*)-3-Benzyloxycarbonylaminohexanol (*ent*-4e). *n*-BuLi (4.83 mL of a 1.4 M solution in hexanes, 6.76 mmol) was added to a solution of di-*iso*-propylamine (0.68 mL, 6.76 mmol) in dry THF (10 mL) at −78 °C and the mixture was stirred for 15 min. The reaction was warmed to 0 °C and $NH_3 \cdot BH_3$ (0.21 g, 6.76 mmol) was added at once. The mixture was stirred for 15 min at 0 °C and for 15 min at rt, after which a solution of **3′e** (0.70 g, 1.69 mmol) in THF (10 mL) was added via cannula at 0 °C and the reaction was stirred for 2 h. Then the reaction was quenched with 1 N HCl (15 mL) and extracted with AcOEt (3×15 mL). The organic fractions were collected, washed

with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and the solvent removed in vacuo affording the wanted γ-amino alcohol ***ent*-4e** (0.26 g, 1.03 mmol) after flash column chromatography purification (hexanes/AcOEt 1:1) in 61% yield. Data for ***ent*-4e**: colorless oil; $[\alpha]_D^{20}$ +5.8 (*c* 0.3, CH_2Cl_2); IR (film): 3308, 1693; ^1H NMR (250 MHz, $CDCl_3$): δ 0.91 (d, *J*=6.7 Hz, 3H), 1.41 (m, 5H), 1.77 (m, 1H), 3.60 (s, 1H), 3.61 (m, 2H), 3.79 (m, 1H), 5.03 (s, 1H), 5.08 (m, 2H), 7.32 (m, 5H); ^{13}C NMR (50 MHz): δ 13.7, 19.1, 37.4, 38.2, 47.7, 58.6, 66.7, 127.8, 127.9, 128.3, 136.3, 157.2; MS (EI): *m*/*z* 252 (M^+, 6), 233 (12), 149 (18), 142 (5), 91 (100), 84 (7). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.75; H, 8.63; N, 6.17.

4.3.5. (−)-(3*S*)-3-Benzyloxycarbonylaminohexanal (*ent*-5e). This compound was obtained following the general method described in Section 4.2.1 for Swern oxidation starting from alcohol ***ent*-4e** (0.25 g, 0.99 mmol), DMSO (0.43 mL, 3.96 mmol), oxalyl chloride (0.25 mL, 1.98 mmol), and Et_3N (1.00 mL, 9.90 mmol) in 65% yield (0.16 g, 0.65 mmol). Data for ***ent*-5e**: colorless oil; $[\alpha]_D^{20}$ −33.9 (*c* 0.3, CH_2Cl_2); IR (film): 3322, 1702; ^1H NMR (250 MHz, $CDCl_3$): δ 0.90 (dd, *J*=6.7, 7.1 Hz, 3H), 1.40 (m, 4H), 2.59 (d, *J*=5.6 Hz, 2H), 4.07 (m, 1H), 5.06 (m, 3H), 7.32 (m, 5H), 9.73 (s, 1H); ^{13}C NMR (50 MHz): δ 13.6, 19.1, 36.8, 46.7, 48.7, 66.6, 127.9, 128.0, 128.4, 136.3, 155.8, 201.1; MS (EI): *m*/*z* 193 (1), 137 (21), 122 (4), 115 (4), 108 (32), 100 (1), 91 (100), 79 (5), 65 (23), 57 (25).

4.3.6. (5*S*,2*E*)-5-Benzyloxycarbonylaminooct-2-enal (*ent*-7e). This compound was obtained following the general method described in Section 4.2.2 for Wittig reaction starting from aldehyde ***ent*-5e** (0.11 g, 0.44 mmol) and triphenylphosphoranylidenacetaldehyde **6** (0.73 g, 2.20 mmol) in 68% yield (82 mg, 0.30 mmol). Data for ***ent*-7e**: colorless oil; IR (film): 3321, 1705, 1704; ^1H NMR (250 MHz, $CDCl_3$): δ 0.91 (t, *J*=6.3 Hz, 3H), 1.37 (m, 4H), 2.49 (m, 2H), 3.84 (m, 1H), 4.73 (d, *J*=8.7 Hz, 1H), 5.07 (m, 2H), 6.11 (dd, *J*=15.7, 7.9 Hz, 1H), 6.78 (m, 1H), 7.32 (m, 5H), 9.46 (d, *J*=7.9 Hz, 1H); ^{13}C NMR (50 MHz): δ 13.9, 19.0, 37.1, 38.9, 50.2, 66.8, 128.1, 128.7, 135.0, 136.5, 154.2, 156.0, 193.4; MS (EI): *m*/*z* 165 (23), 108 (56), 105 (36), 91 (100), 81 (27), 65 (12).

4.3.7. (+)-(2*S*)-2-Propylpiperidine hydrochloride ((+)-coniine hydrochloride) (*ent*-8e). This compound was obtained following the general method described in Section 4.2.3 for the cascade hydrogenation/deprotection/intramolecular reductive amination process starting from aldehyde ***ent*-7e** (71 mg, 0.26 mmol) in 93% yield (39 mg, 0.24 mmol). Data for ***ent*-8e**: white solid; mp: 213–215 °C (Et_2O); $[\alpha]_D^{20}$ +9.0 (*c* 0.2, EtOH); lit.[9] $[\alpha]_D^{20}$ +9.4 (*c* 0.2, EtOH); IR (film): 3355; ^1H NMR (250 MHz, $CDCl_3$): δ 0.98 (m, 3H), 1.24–2.25 (m, 10H), 3.03 (m, 2H), 3.46 (m, 1H), 8.86 (br s, 2H); ^{13}C NMR (50 MHz): δ 14.0, 18.8, 22.5, 28.3, 29.3, 35.6, 46.4, 57.4; MS (EI): *m*/*z* 112 (100), 99 (15), 85 (42), 81 (13), 70 (25), 56 (2).

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