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A general approach for the asymmetric synthesis of densely substituted piperidines and fully substituted piperidinones employing the asymmetric Mannich reaction as key step†

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Two efficient and alternative protocols for the preparation of highly enantioenriched piperidine structures are reported. We have also developed a simple route to access to fully diastereo- and enantioenriched substituted piperidinones. The key step of all this synthesis relies on a diastereoselective Mannich reaction, employing the readily available aminoalcohol (+)-(*S*,*S*)-pseudoephedrine as a chiral auxiliary, which allows the preparation of β-aminocarbonyl compounds in high yield, diastereo and enantioselectivity and using easy-to-scale protocols.

Introduction

Piperidines represent one of the most common building blocks found in natural products and pharmaceuticals, the piperidine ring being a privileged structure in medicinal chemistry which has generated intensive research, focused on exploiting their interesting attributes as potential drugs.[1] Furthermore, these heterocyclic rings are also of interest in synthetic organic chemistry as chiral auxiliaries and ligands.[2] These facts have raised a lot of synthetic interest, focussed especially on many important efforts directed towards the development of stereocontrolled approaches for the preparation of this class of compound.[3] The typical strategies for building up the piperidine framework are mainly based on ring closing processes, starting from a conveniently functionalized acyclic chiral nonracemic starting material by means of intramolecular reactions. In this context, most common approaches to piperidines involve (i) C–N bond formation by intramolecular lactamization, an aza-Michael reaction or reductive amination, or (ii) C–C bond formation by means of intramolecular Michael-type additions, Mannich reactions, ring-closing metathesis or radical cyclization. Alternatively, other methods have been reported in which the piperidine ring is built up by (iii) the simultaneous formation of two different bonds by classical Diels–Alder cycloaddition chemistry or, in a different approach, enantiopure mono- or disubstituted piperidines can also be obtained by (iv) stereoselective nucleophilic addition to pyridinium salts.

In this context, and in connection with our ongoing program directed toward the design and implementation of new methodologies for the asymmetric synthesis of nitrogen heterocycles,[4] we became interested in developing a direct and modular approach for the enantioselective preparation of piperidines with different substitution patterns by applying the stereocontrolled Mannich reaction using (+)-(*S*,*S*)-pseudoephedrine as a chiral auxiliary.[5,6] We suggested that this methodology which had been previously developed in our group could be a successful key step with regard to the stereocontrol in the synthesis of the target compounds (Scheme 1).

In particular, we wish to report herein our synthetic studies toward the direct access to 2,3-disubstituted piperidines and to 3,4,5,6-tetrasubstituted piperidin-2-ones starting from the corresponding Mannich adducts, prepared by our previously mentioned methodology.[5] To access 2,3-disubstituted piperidines, we will present two alternative approaches which involve the use of either ring-closing metathesis or lactamization/reduction reactions for building up the piperidine skeleton and with the two substituents of the final piperidine ring incorporated initially in the stereocontrolled Mannich reaction. Alternatively, we have also developed a more elaborated route to form densely functionalized tetrasubstituted piperidin-2-ones, starting from the same Mannich adducts by using a diastereoselective intramolecular Michael reaction for the construction of the heterocyclic ring, in an approach which has not been reported in the literature for the preparation of piperidines. This second synthetic route has also allowed us to carry out the preparation of both 3,4,5,6-tetrasubstituted and 3,4,5-trisubstituted piperidin-2-ones as highly diastereo- and enantioenriched compounds by carefully selecting the nature of the

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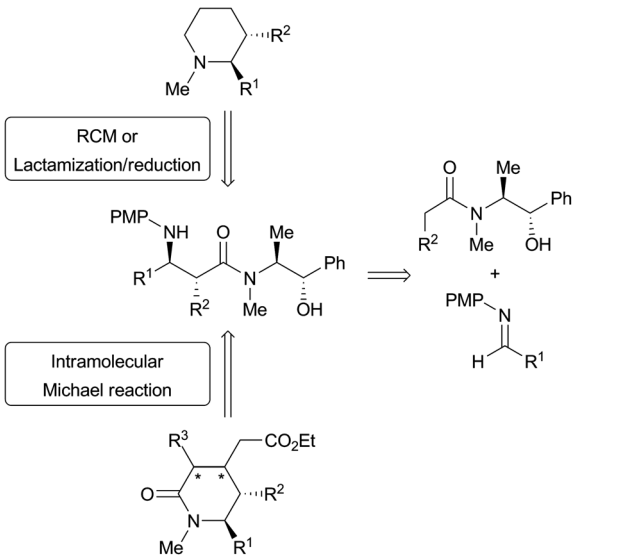
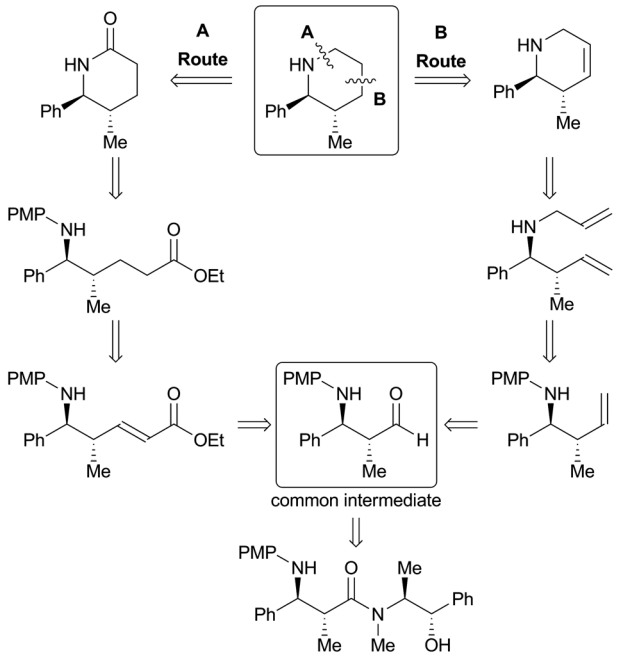
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C-NMR spectra of all prepared compounds. See DOI: 10.1039/c3ra45110k



Scheme 1 Asymmetric synthesis of differently substituted pyrrolidines by applying the stereocontrolled Mannich reaction using (+)-(*S*,*S*)-pseudoephedrine as chiral auxiliary in the key step.



Scheme 2 Two alternative retrosynthetic plans for the synthesis of 2,3-disubstituted piperidines.

reagents used in the intramolecular Michael reaction that builds up the heterocyclic framework.

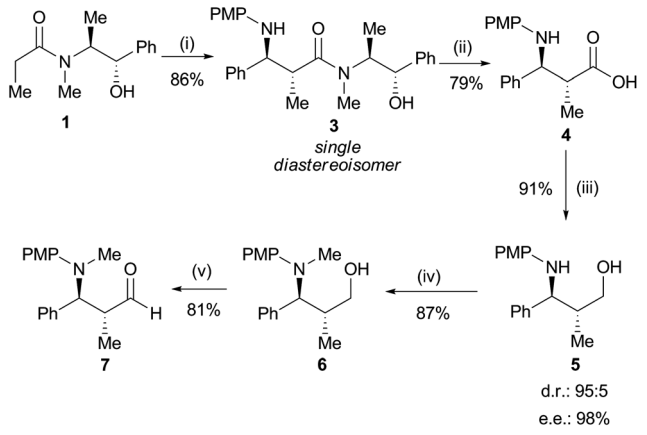
Results and discussion

Asymmetric synthesis of 2,3-disubstituted piperidines

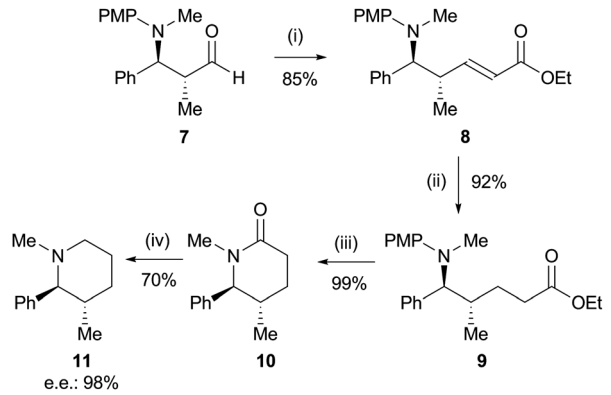
As mentioned in the introduction, access to the target disubstituted piperidines was planned according to two possible approaches which are depicted in the retrosynthetic analysis shown in Scheme 2. Our first approach (route A) consisted of building up the piperidine skeleton from a conveniently substituted δ-amino ester intermediate by means of a lactam formation/reduction protocol. This δ-amino ester should be accessible from a β-amino aldehyde precursor, by simple Wittig-type olefination followed by hydrogenation, and this compound could be obtained starting from the corresponding Mannich adduct, the latter being accessible through our previously mentioned methodology which involves the use of (*S*,*S*)-(+)-pseudoephedrine as a chiral auxiliary. An alternative approach to the same piperidine compounds (route B) could also be envisaged by applying a ring-closing metathesis reaction for the construction of the piperidine framework, for which a conveniently functionalized *N*-allyl amine incorporating an olefin moiety at the correct position could be used as the key intermediate. This intermediate should also be, in principle, readily accessible from the same β-amino aldehyde used in the previous synthetic route *via* olefination and *N*-alkylation.

We started our work by carrying out the Mannich reaction between (*S*,*S*)-(+)-pseudoephedrine propionamide **1** and imine **2**. Under our reported conditions, adduct **3** was isolated in an excellent yield and as a single *anti* diastereoisomer with a very high facial selectivity (Scheme 3).[7] We next faced the conversion of the β-amino amide adduct **3** into the corresponding β-amino aldehyde, which was proposed as the key compound for the two synthetic approaches proposed in Scheme 2. The direct controlled reduction of the amide moiety, in order to obtain a formyl group, by using different reducing systems was unsuccessful, so we moved to an alternative procedure that involved a hydrolysis/reduction sequence. Thus, acid hydrolysis of β-amino amide **3** under known conditions followed by standard borane-mediated reduction led to the formation of the γ-amino alcohol **5** in good yield after flash column chromatography purification and with no epimerization at any stereocentre, as NMR analysis of the crude reaction mixture indicated. At this point, we were also able to check the optical purity of the obtained amino alcohol by HPLC analysis on a chiral stationary phase under conditions previously optimized for a racemic standard (see the ESI† for details). The next step involved the oxidation of γ-amino alcohol **5** to the target amino aldehyde, but after several unsuccessful attempts using various reaction conditions we were not able to obtain the desired aldehyde due to extensive product decomposition. In order to overcome this stability problem attributed to the presence of a secondary amino group, we proceeded to carry out the *N*-methylation of **5**, obtaining derivative **6** in an excellent yield, which was next subjected to IBX-mediated oxidation under conditions previously optimized in our group.[8] Under these conditions, a clean reaction took place, delivering the β-amino aldehyde **7** in an excellent yield.

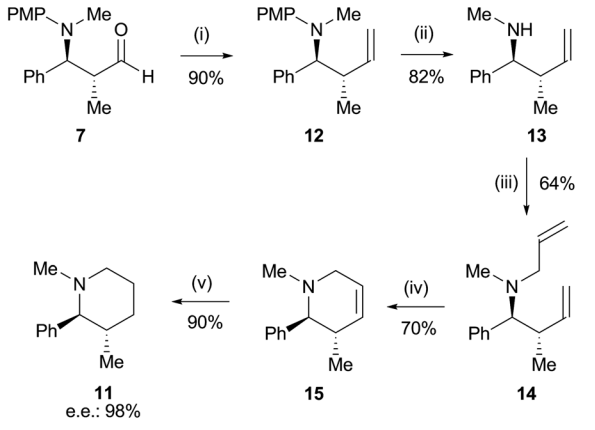
At this point, we proceeded first to evaluate the synthetic route which involved the formation of the piperidine ring by lactamization/reduction, as planned in route A, shown in Scheme 2. We therefore subjected β-amino aldehyde **7** to a Wittig olefination reaction with the suitable and commercially available $Ph_3P{=}CHCO_2Et$, which allowed us to obtain the corresponding conjugated α,β-unsaturated δ-amino ester **8** in an



Scheme 3 *Reagents and Conditions*: (i) (1) LDA, LiCl, THF, −78 °C; (2) PhCH=NPMP (**2**), 0 °C. (ii) H_2SO_4 (4 M), 1,4-dioxane, 0 °C to reflux. (iii) BH_3–Me_2S, THF, r.t. (iv) (1) HCHO, CH_3CN, r.t.; (2) $NaBH_4$, TFA, 0 °C to r.t. (v) IBX, EtOAc, reflux, 3 h.



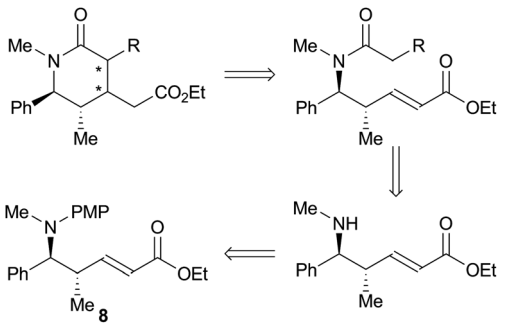
Scheme 4 *Reagents and Conditions*: (i) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, r.t., 5 h. (ii) H_2, PtO_2 (10 mol%), EtOAc, r.t., 1 h. (iii) (1) CAN, H_2SO_4 (concd.), CH_3CN–H_2O (3 : 1), 0 °C, 90 min. (2) NaOH, r.t., 2 h. (iv) LAH, Et_2O, 0 °C, 1 h.



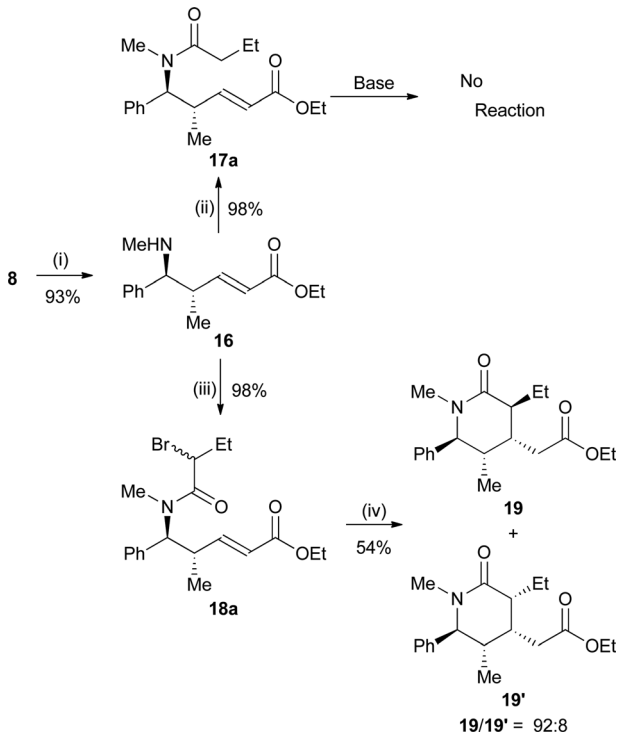
Scheme 5 *Reagents and Conditions*: (i) 5-methylsulfonyl-1-phenyl-1*H*-tetrazole, $KN(SiMe_3)_2$, toluene, −20 °C, 90 min. (ii) CAN, H_2SO_4 (concd.), CH_3CN–H_2O (3 : 1), 0 °C, 90 min. (iii) $CH_2{=}CHCH_2I$, K_2CO_3, CH_3CN, reflux, 4 h. (iv) (1) HCl (concd.), Et_2O, 30 min. (2) 2nd generation Grubbs cat. (5 mol%), CH_2Cl_2, reflux, 1 h. (v) H_2, PtO_2 (10 mol%), EtOAc, r.t., 1 h.

excellent yield and as a single *E* diastereoisomer (Scheme 4). A subsequent standard hydrogenation in the presence of 10 mol% PtO_2 delivered the δ-amino ester **9**. Next, we proceeded to remove the *p*-methoxyphenyl group under oxidative conditions, which proceeded smoothly and delivered directly the piperidinone **10** after an intramolecular amide formation, which took place *in situ* on the secondary amine intermediate after basification. Finally, the 2,3-disubstituted piperidine **11** was obtained after a reduction step using LAH in an overall yield of 54% starting from β-amino aldehyde **7** (4 steps) and of 25% if calculated from (*S*,*S*)-(+)-pseudoephedrine propionamide **1** (9 steps). It should be pointed out that NMR analysis of the crude reaction mixtures of all the transformations carried out from **7** indicated that no epimerization had taken place at any stereocentre present in these compounds. In addition, we also measured the optical purity of the final piperidine **11** by chiral HPLC, under conditions optimized for a racemic standard, observing that it had been obtained in 98% ee which matched with the optical purity of the previous γ-amino alcohol **5**.

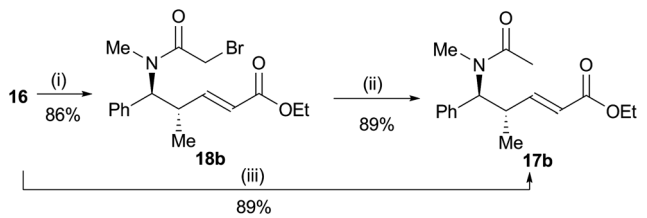
We next evaluated the second approach to piperidine **11** according to the alternative route B depicted in Scheme 2, which involved ring construction by ring closing metathesis (Scheme 5). We started by surveying the Wittig methylenation of β-amino aldehyde **7** using methylenetriphenylphosphorane, which should be generated *in situ* starting from the commercially available phosphonium salt and a suitable base. However, all our attempts were unsuccessful, which was attributed in this case to the incompatibility of the starting β-amino aldehyde with the presence of a strongly basic reagent such as the phosphorous ylide employed. For this reason, we moved to the Julia-Kocienski protocol[9] and therefore we proceeded to prepare the required tetrazolyl sulfone anion as described in the literature[10] and reacted this with aldehyde **7**, furnishing the target olefination product **12** in an excellent 90% yield. Removal of the PMP group and subsequent *N*-allylation reaction furnished the diene **14** in an excellent yield. With this compound in hand, we proceeded to carry out the ring-closing metathesis reaction under different reaction conditions, which included the use of both first and second generation Grubbs catalysts. However, in all our attempts no reaction was observed and the starting material was recovered unchanged under all the conditions tested, which also involved carrying out the reaction in boiling solvents and for prolonged reaction times. We attributed this lack of reactivity to catalyst poisoning by the tertiary amine moiety, because of its ability to coordinate to the intermediate metal–alkylidene complex and consequently, we decided to carry out the metathesis reaction on the corresponding ammonium hydrochloride,[11] obtained after treating amine **14** with excess HCl in Et_2O and removal of the volatiles. Gratifyingly, under these conditions, tetrahydropiperidine **15** was obtained in a 70% yield after reaction in the presence of the second generation Grubbs catalyst in refluxing dichloromethane. Finally, the hydrogenation of **15** furnished 2,3-disubstitutedpiperidine **11** in a 30% overall yield from the β-amino aldehyde **7** (5 steps) and in 13% from **1** (10 steps). In light of these data, we concluded that our initial approach involving the piperidine ring formation by lactamization/reduction was much more effective than this second approach.



Scheme 6 Retrosynthetic plan for the synthesis of a fully substituted piperidinone ring.



Scheme 7 *Reagents and Conditions*: (i) CAN, H_2SO_4 (concd.), CH_3CN–H_2O (3 : 1), 0 °C, 2 h. (ii) $(n\text{-BuCO})_2O$, DMAP, CH_2Cl_2, r.t., 2 h.; (iii) 2-bromobutyric acid, DCC, DMAP, CH_2Cl_2, r.t., 90 min. (iv) *n*-BuLi, LiCl, THF, −105 °C, 5 min.



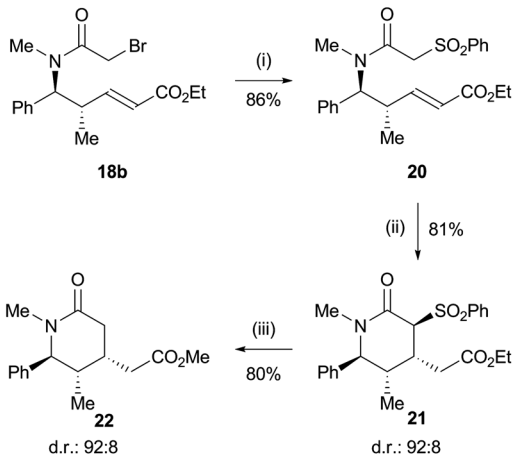
Scheme 8 *Reagents and Conditions*: (i) 2-bromoacetic acid, DCC, DMAP, CH_2Cl_2, r.t., 90 min. (ii) *n*-BuLi, LiCl, THF, −105 °C, 5 min. (iii) Ac_2O, DMAP, CH_2Cl_2, r.t., 2 h.

As we did before, we also confirmed that piperidine **11** was obtained as single diastereoisomer (by NMR analysis of the crude mixture of **11**), which indicated that all the transformations performed in this alternative synthesis also proceeded with no epimerization in any of the stereogenic centres present in any of the compounds employed. In addition, we also verified that the final piperidine **11** had been obtained with the same enantiomeric excess as the one found for the β-amino aldehyde precursor **6** (98% ee).

Asymmetric synthesis of 3,4,5,6-tetrasubstituted piperidin-2-ones

Complex and polysubstituted piperidines and piperidinones are difficult targets to be accessible by classical methods and for this reason we have envisaged a novel synthesis according to retrosynthetic analysis shown in Scheme 6 in which the key step for building up the piperidine skeleton relies on a diastereoselective intramolecular Michael reaction step by using a conveniently substituted *N*-acyl δ-amino α,β-unsaturated ester. This intramolecular reaction would lead to the formation of a piperidin-2-one final compound, together with the concomitant generation of two additional stereocentres and therefore, suitable reaction conditions should be found in order to achieve the highest stereocontrol in their formation. As it can be seen in the following scheme, this key substrate on which the intramolecular Michael reaction was planned to take place can be easily accessed from the δ-amino α,β-unsaturated ester **8**, obtained previously during the synthesis of 2,3-disubstituted piperidines and which is prepared in a diastereo- and enantioselective fashion by our protocol for carrying out the Mannich reaction using (*S*,*S*)-(+)-pseudoephedrine as a chiral auxiliary.[5]

We started our work as depicted in Scheme 7 by removing the PMP group from the δ-amino α,β-unsaturated ester **8** using the same reaction conditions as previously employed. Next, the obtained secondary amine was acylated with *n*-butyric anhydride, isolating *N*-butanoyl *N*-methyl δ-amino α,β-unsaturated ester **17a** in excellent yield. Disappointingly, when this compound was subjected to the projected intramolecular Michael addition using different bases and conducting the reaction at different temperatures in order to generate the required enolate intermediate, no reaction was observed, recovering the starting material unchanged in all cases. We supposed that this lack of reactivity could be due to the difficulties in the formation of the enolate intermediate and, in order to verify this hypothesis, we proceeded to quench the reaction with external highly reactive electrophiles such as MeI or benzaldehyde, also recovering unchanged starting material. Thus, we decided to generate the required nucleophilic species by a halogen–lithium exchange, preparing the corresponding α-bromo amide **18a** by acylation of **16** with commercially available 2-bromobutyric acid. Reacting this compound **18a** with *n*-BuLi in THF at low temperature resulted in a very fast reaction, furnishing the desired piperidin-2-one **19** in a moderate yield (52%) and as an 80 : 20 mixture of diastereoisomers, with regard to the relative configuration of the stereocentre at C3 (**19** and **19′**). Importantly, other possible diastereoisomers that could be eventually produced were not detected after NMR analysis of the crude reaction mixture.



Scheme 9 *Reagents and Conditions*: (i) $NaSO_2Ph$, DMF, r.t., 1 h. (ii) NaH, THF, −40 °C, 3 h. (iii) Mg, MeOH, 0 °C to r.t., 5 h.

Moreover, the diastereoselectivity of the reaction could be significantly improved by incorporating LiCl as an additive to the reaction scheme, leading to the formation of piperidin-2-one **19** almost as a single diastereoisomer in a 54% yield (**19**/**19′** ratio: 92 : 8 by NMR analysis of crude reaction mixture).

Asymmetric synthesis of 4,5,6-trisubstituted piperidin-2-ones

In light of the results obtained when trying to access to the piperidine skeleton by an intramolecular Michael reaction, we also decided to survey the possibility of optimizing a synthetic route to 4,5,6-trisubstituted piperidin-2-ones, by using the corresponding *N*-bromoacetyl δ-amino α,β-unsaturated ester as a substrate for undergoing the cyclization step (Scheme 8). In this context, acylation of **16** with bromoacetic acid under the same reaction conditions led to the formation of the required *N*-bromoacetamide **18b** but, when we tested the subsequent intramolecular Michael reaction through formation of the nucleophile *via* a lithium–halogen exchange, no cyclization reaction was observed, isolating the debrominated *N*-acetyl derivative **17b**, almost quantitatively. This compound could also be easily obtained from **16** in an 86% yield by acetylation. In addition, we tried the cyclization reaction starting from **17b**, by forming the required enolate through conventional deprotonation procedures, without any success in all our attempts.

Therefore, we modified our synthetic approach by activating the Michael donor site of the starting material by incorporating a second electron-withdrawing group which would enhance the acidity of the α-protons and hence would favour the formation of the nucleophile participating in the intramolecular Michael reaction. In particular, we decided to introduce a sulfone moiety which, after the cyclization step, could be easily removed by conventional reductive cleavage methods (Scheme 9). Therefore, we started with the conversion of the previously synthesized bromoamide **18b** into sulfone **20** by reaction with $NaSO_2Ph$, sulfone **20** underwent a clean and efficient intramolecular Michael reaction upon treatment with sodium hydride, delivering piperidin-2-one **21** in an excellent yield (81%) and as almost diastereopure material, as NMR analysis of the crude reaction mixture indicated. Finally, the target trisubstituted pyrrolidin-2-one **22** was achieved by desulfonylation using Mg in MeOH as the corresponding methyl ester.[12]

Conclusions

To sum up, we have demonstrated that the Mannich reaction could be a reliable tool for the asymmetric synthesis of nitrogen containing six-membered heterocycles such as piperidines and piperidinones, starting from β-amino carbonyl compounds. We have shown two efficient and straightforward routes to access diastereo- and enantiomerically pure piperidines, employing simple transformations in an excellent overall yield and maintaining the excellent diastereo- and enantiopurity obtained during the Mannich reaction. Furthermore, we have accessed a polysubstituted piperidinone core, in which two new stereogenic centres are formed in a highly diastereoselective way, demonstrating the ability of the preexisting stereogenic centres to control the stereochemical outcome of this reaction in a very efficient way. Importantly, these methodologies constitute important alternatives to the classical strategies for the construction of such heterocycles.

Experimental section

General information

NMR spectra were recorded at 20–25 °C, running at 300 MHz for ^1H and at 75 MHz for ^{13}C in $CDCl_3$ solutions and the resonances are reported in ppm relative to tetramethylsilane, unless otherwise stated. The following abbreviations were used to designate the chemical shift multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, bs = broad signal. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad signal (bs). Assignments of individual signals were carried out using COSY, HMQC and DEPT experiments. IR spectra were measured in the interval between 4000 and 400 cm^{-1}, obtained by depositing a film on a KBr plate and only the characteristic bands are given. Mass spectra were recorded under electron impact (EI) or chemical ionization (CI) at 70 eV. The obtained data are presented in mass units (*m*/*z*) and the values found in the brackets belong to the relative intensities, compared to the base peak (100%). Optical rotations were measured at 20 °C and recorded on solution on a 1 dm length cell using a Na lamp (589 nm) in the solvent and concentration indicated in each case. TLC was carried out with 0.2 mm thick silica gel plates and visualization was accomplished by ultraviolet irradiation light or by spraying with phosphomolybdic acid. Flash column chromatography on silica gel was performed with silica gel (230–400 mesh). All solvents used in the reactions were dried and purified according to standard

procedures. All other reagents were used as purchased. All air- or moisture-sensitive reactions were performed under an argon atmosphere. The glassware was oven dried (140 °C) overnight and purged with argon prior to use. Enantiomeric excesses (ee) were determined by HPLC under the conditions specified in each case.

(2*R*,3*S*)-3-(4-Methoxyphenylamino)-2-methyl-3-phenylpropanoic acid (4)

4 M H_2SO_4 (10 mL) was slowly added to a cooled (0 °C) solution of amide **3** (0.25 g, 0.58 mmol) in 1,4-dioxane (10 mL). The reaction was refluxed for 6 h after which it was cooled down to r.t. Water (20 mL) was added and the mixture was carefully basified to pH = 4 and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure affording β-amino acid **4** (0.13 g, 0.45 mmol) as a colorless oil, without further purification. Yield: 79%. $[\alpha]_D^{20} = -112.0$ (c = 1.0, CH_2Cl_2). IR (neat): 1510 (C=O), 3418 (OH + NH) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.10 (d, 3H, J = 7.0 Hz, CH_3CH), 2.75–293 (m, 1H, CHCO), 3.68 (s, 3H, CH_3O), 4.38 (d, 1H, J = 9.1 Hz, CHN), 5.80–6.50 (br, 2H, NH + OH), 6.53–6.62 (m, 2H, C_{arom}–H), 6.63–6.73 (m, 2H, C_{arom}–H), 7.15–7.35 (m, 5H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 15.0 (*C*H_3CH), 45.9 (*C*HCO), 55.6 (CHN), 63.1 (CH_3O), 114.6, 116.9, 127.1, 127.7, 128.7 (C_{arom}–H), 139.3, 140.1, 153.3 (C_{arom}–C), 179.5 (CO). MS (EI) [m/z (rel. abundance)]: 285 (M^+, 100), 212 (49), 197 (69), 168 (35), 122 (73), 91 (79), 77 (79), 58 (3). HRMS: m/z calculated for $[C_{17}H_{19}NO_3]^+$: 285.1365; found: 285.1387.

(2*R*,3*S*)-3-(4-Methoxyphenylamino)-2-methyl-3-phenylpropan-1-ol (5)

Borane-dimethyl sulfide complex (2.0 M in THF) (0.52 mL, 1.05 mmol) was added to a solution of β-amino acid **4** (0.10 g, 0.35 mmol) in THF (10 mL). The reaction was maintained stirring for 4 h at r.t. after which water was added to quench the reaction and it was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure affording pure γ-amino alcohol **5** (0.07 g, 0.27 mmol) as a yellowish oil after flash column chromatography (hexanes–EtOAc 6 : 4). Yield: 80% (dr: >95 : 5). The ee was determined by HPLC using Chiralpak IA column, [*n*-hexane–i-PrOH (95 : 5)]; flow rate 1.00 mL min^{-1}; τ_{major} (2*R*,3*S*) isomer = 24.40 min; τ_{minor} (2*S*,3*R*) isomer = 23.05 min (98% ee). $[\alpha]_D^{20} = -67.8$ (c = 1.0, CH_2Cl_2). IR (neat): 3376 (OH + NH) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.82 (d, 3H, J = 6.9 Hz, CH_3CH), 2.00–2.23 (m, 1H, C*H*CH_3), 3.60–3.98 (m, 5H, CH_3O + CH_2OH), 4.20 (d, 1H, J = 7.8 Hz, CHN), 6.50–6.60 (m, 2H, C_{arom}–H), 6.64–6.73 (m, 2H, C_{arom}–H), 7.15–7.35 (m, 5H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.7 (*C*H_3CH), 41.2 (*C*HCH_2), 55.7 (CHN), 65.2 (CH_3O), 67.4 (CH_2O), 114.7, 116.3, 127.0, 127.1, 128.5 (C_{arom}–H), 142.3, 143.1, 153.0 (C_{arom}–C). MS (EI) [m/z (rel. abundance)]: 271 (M^+, 88), 213 (100), 212 (94), 197 (77), 168 (67), 134 (79), 108 (55), 91 (97), 77 (40), 57 (51). HRMS: m/z calculated for $[C_{17}H_{21}NO_2]^+$: 271.1572 (M^+); found: 271.1566.

(2*R*,3*S*)-3-[*N*-(4-Methoxyphenyl)-*N*-methylamino]-2-methyl-3-phenylpropan-1-ol (6)

Formaldehyde (1.79 mL, 22.14 mmol) was added to a solution of alcohol **5** (1.27 g, 4.70 mmol) in CH_3CN (20 mL). The reaction was maintained stirring for 2 h at r.t. after which water was added to quench the reaction and it was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure, affording pure (4*S*,5*R*)-3-(4-methoxyphenyl)-5-methyl-4-phenyl-1,3-oxazinane (1.34 g, 4.70 mmol) after flash column chromatography (hexanes–EtOAc 9 : 1). Yield: 99%. $[\alpha]_D^{20}$ = +27.4 (c = 1.0, CH_2Cl_2. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.68 (d, 3H, J = 6.7 Hz, CH_3CH), 2.09–2.30 (m, 1H, C*H*CH_3), 3.41 (dd, 1H, J = 11.0, 11.0 Hz, CHCH_aH$_b$O), 3.66 (s, 3H, CH_3O), 3.73 (d, 1H, J = 9.2 Hz, CHN), 4.13 (dd, 1H, J = 4.4, 11.0 Hz, CHCH_aH$_b$O), 4.40 (d, 1H, J = 8.7 Hz, CH_aH$_b$N), 4.81 (d, 1H, J = 8.7 Hz, CH_aH$_b$N), 6.64 (d, 2H, J = 8.8 Hz, C_{arom}–H), 6.94 (d, 2H, J = 8.8 Hz, C_{arom}–H), 7.06–7.32 (m, 5H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 13.8 (*C*H_3CH), 36.5 (*C*HCH_3), 55.2 (CHNH), 70.9 (CH_3O), 73.7 (CH*C*H_2O), 87.0 (CH_2N), 113.8, 126.0, 127.0, 128.0, 128.6 (C_{arom}–H), 140.4, 140.6, 156.0 (C_{arom}–C). MS (CI) [m/z (rel. abundance)]: 283 [($M + H)^+$, 100), 269 (16), 265 (20), 211 (32), 136 (22). HRMS: m/z calculated for $[C_{18}H_{21}NO_2]^+$: 283.1572 [$(M + H)^+$]; found: 283.1566.

Next, a solution of (4*S*,5*R*)-3-(4-methoxyphenyl)-5-methyl-4-phenyl-1,3-oxazinane (1.34 g, 4.70 mmol) in CH_2Cl_2 (20 mL) was carefully added to a cooled (0 °C) suspension of $NaBH_4$ (0.89 g, 23.60 mmol) and trifluoroacetic acid (10.9 mL, 141.50 mmol). The reaction was warmed to r.t. and maintained for 2 h after which it was cooled down to 0 °C. The mixture was carefully basified with NaOH 4 M to pH = 14 and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure affording alcohol **6** (1.20 g, 4.20 mmol) as a pure compound after flash column chromatography (hexanes–EtOAc 9 : 1). Yield: 88%. $[\alpha]_D^{20} = -208.3$ (c = 1.0, CH_2Cl_2). IR (neat): 3398 (OH + NH) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.73 (d, 3H, J = 6.7 Hz, CH_3CH), 2.45 (s, 3H, CH_3N), 2.56–2.77 (m, 1H, C*H*CH_3), 3.76 (s, 3H, CH_3O), 3.84–3.97 (m, 2H, CH_2O), 4.33 (d, 1H, J = 11.2 Hz, CHN), 6.75–6.95 (m, 6H, C_{arom}–H), 7.19–7.29 (m, 3H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 15.2 (*C*H_3CH), 33.1 (*C*HCH_3), 33.4 (CH_3N), 55.5 (CHN), 69.7 (CH_2O), 75.6 (CH_3O), 114.2, 121.0, 127.4, 127.8, 128.7 (C_{arom}–H), 135.0, 145.1, 154.2 (C_{arom}–C). MS (EI) [m/z (rel. abundance)]: 285 (M^+, 9), 227 (18), 226 (100), 211 (12), 196 (16), 136 (7), 122 (8), 117 (5), 91 (16). HRMS: m/z calculated for $[C_{18}H_{23}NO_2]^+$: 285.1729 (M^+); found: 285.1718.

(2*R*,3*S*)-3-[*N*-(4-Methoxyphenyl)-*N*-methylamino]-2-methyl-3-phenylpropanal (7)

IBX (1.35 g, 4.84 mmol) was added to a solution of alcohol **6** (0.46 g, 1.61 mmol) in EtOAc (20 mL) and the reaction mixture was refluxed. After 2 h it was cooled to r.t., filtered and the solvent removed under reduced pressure. The crude mixture was purified by flash column chromatography (hexanes–EtOAc 9 : 1) affording pure product **6** (0.37 g, 1.30 mmol) as a colorless

oil. Yield: 81%. $[\alpha]_D^{20} = -145.6$ ($c = 1.0$, CH_2Cl_2). IR (neat): 1507 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.01 (d, 3H, $J = 6.8$ Hz, CH_3CH), 2.51 (s, 3H, CH_3N), 3.17–3.35 (m, 1H, CHCH$_3$), 3.76 (s, 3H, CH_3O), 4.79 (d, 1H, $J = 11.3$ Hz, CHN), 6.79–6.84 (m, 4H, C_{arom}–H), 6.98–7.06 (m, 2H, C_{arom}–H), 7.20–7.35 (m, 3H, C_{arom}–H), 9.78 (d, 1H, $J = 4.4$ Hz, CHO). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.6 (*C*H$_3$CH), 33.0 (CH_3N), 46.6 (*C*HCH$_3$), 55.5 (CHN), 68.9 (CH_3O), 114.3, 119.7, 127.7, 128.2 (C_{arom}–H), 134.7, 144.6, 153.8 (C_{arom}–C), 203.4 (CHO). MS (EI) [*m*/*z* (rel. abundance)]: 283 (M^+, 9), 265 (11), 226 (24), 147 (100), 137 (84), 129 (15), 123 (30), 107 (13). HRMS: *m*/*z* calculated for $[C_{18}H_{21}NO_2]^+$: 283.1572 (M^+); found: 283.1581.

(4*S*,5*S*,*E*)-Ethyl 5-[*N*-(4-methoxyphenyl)-*N*-methylamino]-4-methyl-5-phenylpent-2-enoate (8)

Carbethoxymethylene triphenylphosphorane (0.54 g, 1.69 mmol) was added to a solution of aldehyde **7** (0.09 g, 0.34 mmol) in CH_2Cl_2 (20 mL). The reaction was maintained stirring for 5 h at r.t. after which water was added to quench the reaction and it was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure affording pure ester **8** (0.10 g, 0.28 mmol) after flash column chromatography (hexanes–EtOAc 8 : 2). Yield: 85% (*E*–*Z* = >15 : 1). $[\alpha]_D^{20} = -98.3$ ($c = 1.0$, CH_2Cl_2). IR (neat): 1716 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.99 (d, 3H, $J = 6.6$ Hz, CH_3CH), 1.28 (*t*, 3H, $J = 7.1$ Hz, CH_3CH$_2$), 2.52 (s, 3H, CH_3N), 3.13–3.32 (m, 1H, CHCH$_3$), 3.75 (s, 3H, CH_3O), 4.18 (q, 2H, $J = 7.1$ Hz, CH_2CH$_3$), 4.48 (d, 1H, $J =$ 10.7 Hz, CHN), 5.95 (dd, 1H, $J = 0.84$, 14.8 Hz, CH=CHCO), 6.74–6.84 (m, 4H, C_{arom}–H), 7.05–7.35 (m, 6H, C_{arom}–H + CHCO). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.3 (*C*H$_3$CH), 17.9 (*C*H$_3$CH$_2$), 32.8 (CH_3N), 37.5 (*C*HCH$_3$), 55.6 (CHN), 60.2 (*C*H$_2$CH$_3$), 71.2 (CH_3O), 114.3 (C*H*=CHCO), 118.5 (CHCO), 120.7, 127.3, 128.0, 128.1 (C_{arom}–H), 136.8, 145.2, 152.9 (C_{arom}–C), 166.6 (CO). MS (EI) [*m*/*z* (rel. abundance)]: 353 (M^+, 2), 227 (14), 226 (100), 196 (14), 91 (2). HRMS: *m*/*z* calculated for $[C_{22}H_{27}NO_3]^+$: 353.1991 (M^+); found: 353.1985.

(4*S*,5*S*)-Ethyl 5-[*N*-(4-methoxyphenyl)-*N*-methylamino]-4-methyl-5-phenylpentanoate (9)

A solution of ester **8** (0.10 g, 0.28 mmol) in EtOAc (10 mL) was stirred in the presence of PtO_2 (10 mg, 10 mol%) under a H_2 atmosphere (balloon) at r.t. for 1 h. Next, the mixture was filtered and the solvent removed under reduced pressure. Compound **9** (0.09 g, 0.26 mmol) was obtained as a colorless oil after flash column chromatography purification (hexanes–EtOAc 9 : 1). Yield: 92%. $[\alpha]_D^{20} = -130.4$ ($c = 1.0$, CH_2Cl_2). IR (neat): 1639 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.83 (d, 3H, $J = 6.5$ Hz, CH_3CH), 1.27 (*t*, 3H, $J = 7.1$ Hz, CH_3CH$_2$), 1.42–1.60 (m, 1H, CHCH$_3$), 2.22–2.54 (m, 4H, CH_2CH_2), 2.54 (s, 3H, CH_3N), 3.76 (s, 3H, CH_3O), 4.15 (q, 2H, $J = 7.1$ Hz, CH_2CH$_3$), 4.30 (d, 1H, $J = 10.6$ Hz, CHN), 6.70–6.86 (m, 4H, C_{arom}–H), 7.00–7.10 (m, 2H, C_{arom}–H), 7.15–7.30 (m, 3H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.3 (*C*H$_3$CH), 17.1 (*C*H$_3$CH$_2$), 29.0 (*C*H$_2$CH$_2$CO), 32.0 (*C*H$_2$CO), 32.4 (CH_3N), 55.6 (CHN), 55.6 (*C*HCH$_3$), 60.3 (*C*H$_2$CH$_3$), 71.2 (CH_3O), 114.4, 117.5, 126.9, 127.9, 128.1 (C_{arom}–H), 137.9, 145.5, 152.3 (C_{arom}–C), 173.9 (CO). MS (EI) [*m*/*z* (rel. abundance)]: 355 (M^+, 5), 226 (100), 196 (11), 83 (12). HRMS: *m*/*z* calculated for $[C_{22}H_{29}NO_3]^+$: 355.2147 (M^+); found: 355.2139.

(5*S*,6*S*)-1,5-Dimethyl-6-phenylpiperidin-2-one (10)

Cerium ammonium nitrate (0.46 g, 0.85 mmol) and H_2SO_4 (60 μL) were added to a cooled (0 °C) solution of **9** (0.10 g, 0.28 mmol) in a mixture of CH_3CN–H_2O 3 : 1 (20 mL) and it was stirred for 90 minutes at this temperature, after which NaOH 4 M was added until pH = 12. After stirring the biphasic mixture at r.t. for further 2 h, it was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were collected, dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. Compound **10** (0.06 g, 0.28 mmol) was obtained as a colorless oil after flash column chromatography purification (hexanes–EtOAc 2 : 8). Yield: 99%. $[\alpha]_D^{20} = -11.7$ ($c = 1.0$, CH_2Cl_2). IR (neat): 1631 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.95 (d, 3H, $J = 6.6$ Hz, CH_3CH), 1.40–1.60 (m, 1H, CHCH$_3$), 1.72–1.95 (m, 2H, CH_2CH), 2.35–2.60 (m, 2H, CH_2CO), 2.64 (s, 3H, CH_3N), 3.91 (d, 1H, $J = 7.3$ Hz, CHN), 7.05–7.20 (m, 2H, C_{arom}–H), 7.21–7.40 (m, 3H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 18.4 (*C*H$_3$CH), 26.6 (*C*H$_2$CH), 31.0 (CH_2CO), 33.6 (*C*HCH$_3$), 37.0 (CH_3N), 71.1 (CHN), 127.0, 127.7, 128.7 (C_{arom}–H), 141.1 (C_{arom}–C), 170.8 (CO). MS (EI) [*m*/*z* (rel. abundance)]: 203 (M^+, 3), 118 (3), 87 (8), 85 (55), 83 (100), 83 (3). HRMS: *m*/*z* calculated for $[C_{13}H_{17}NO]^+$: 203.1310 (M^+); found: 203.1314.

(1*S*,2*S*)-*N*,2-Dimethyl-*N*-(4-methoxyphenyl)-1-phenylbut-3-en-1-amine (12)

Potassium hexamethyldisilazide (0.5 M in toluene, 3.3 mL, 1.65 mmol) was added dropwise for 30 minutes to a cooled (−20 °C) solution of **7** (0.13 g, 0.46 mmol) and sulfone (0.14 g, 0.63 mmol)[9] in THF (10 mL) and it was stirred for 1 h at this temperature, after which H_2O (20 mL) was added. The mixture was extracted with EtOAc (3 × 15 mL) and the combined organic layers were collected, dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. Compound **12** (0.11 g, 0.41 mmol) was obtained as a colorless oil after flash column chromatography purification (hexanes–EtOAc 9.5 : 0.5). Yield: 90%. $[\alpha]_D^{20} = -205.7$ ($c = 1.0$, CH_2Cl_2). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.98 (d, 3H, $J = 6.6$ Hz, CH_3CH), 2.59 (s, 3H, CH_3N), 3.00–3.17 (m, 1H, CHCH$_3$), 3.77 (s, 3H, CH_3O), 4.47 (d, 1H, $J = 10.7$ Hz, CHN), 5.07 (d, 1H, $J_{cis} = 10.3$ Hz, CH_{cis}H$_{trans}$=CH), 5.19 (d, 1H, $J_{trans} = 17.2$ Hz, CH$_{cis}$H$_{trans}$=CH), 6.05 (ddd, 1H, $J = 7.7$, 10.3, 17.2 Hz, CH$_2$=CH), 6.75–6.87 (m, 4H, C_{arom}–H), 7.10–7.19 (m, 2H, C_{arom}–H), 7.20–7.34 (m, 3H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 18.5 (*C*H$_3$CH), 32.4 (CH_3N), 38.5 (*C*HCH$_3$), 55.6 (CHN), 70.6 (CH_3O), 113.8 (CH_2), 114.4 (CH_2*C*H), 117.0, 127.0, 128.0, 128.1 (C_{arom}–H), 138.0 (C_{arom}–C), 142.5 (C_{arom}–H), 145.4, 152.2 (C_{arom}–C). MS (EI) [*m*/*z* (rel. abundance)]: 281 (M^+, 2), 226 (100), 211 (14), 196 (19), 167 (4), 129 (4), 122 (4). HRMS: *m*/*z* calculated for $[C_{19}H_{23}NO]^+$: 281.1780 (M^+); found: 281.1792.

(1*S*,2*S*)-*N*,2-Dimethyl-1-phenylbut-3-en-1-amine (13)

Cerium ammonium nitrate (0.70 g, 1.24 mmol) and H_2SO_4 (77 μL) were added to a cooled (0 °C) solution of **12** (0.12 g, 0.41 mmol) in a mixture of CH_3CN–H_2O 3 : 1 (20 mL) and it was stirred for 90 minutes at this temperature, after which NaOH 4 M was added until pH = 12. After stirring the biphasic mixture at r.t. for further 2 h, it was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were collected, dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. Pure compound **13** (0.06 g, 0.33 mmol) was obtained as a yellowish oil without further purification. Yield: 82%. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.78 (d, 3H, J = 6.8 Hz, CH_3CH), 1.60–2.00 (bs, 1H, NH), 2.17 (s, 3H, CH_3N), 2.26–2.45 (m, 1H, CHCH$_3$), 3.13 (d, 1H, J = 8.9 Hz, CHN), 5.07 (dd, 1H, J = 10.1, 1.6 Hz, CH_{cis}H$_{trans}$), 5.16 (dd, 1H, J = 17.1, 1.1 Hz, CH$_{cis}H_{trans}$), 5.71 (ddd, 1H, CH$_2$=CH), 7.18–7.38 (m, 5H, C$_{arom}$–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 17.9 (*C*H$_3$CH), 34.7 (CH_3N), 45.6 (*C*HCH$_3$), 70.1 (CHN), 115.9 (CH_2), 127.1, 128.1, 128.2 (C$_{arom}$–H), 142.2 (*C*$_{arom}$–C), 142.3 (CH$_2$*C*H). MS (CI) [*m*/*z* (rel. abundance)]: 176 [(M + H)$^+$, 18), 174 (23), 145 (62), 121 (13), 120 (100), 98 (5). HRMS: *m*/*z* calculated for [$C_{12}H_{18}N$]$^+$: 176.1439 [(M + H)$^+$]; found: 176.1444.

(1*S*,2*S*)-*N*-Allyl-*N*,2-dimethyl-1-phenylbut-3-en-1-amine (14)

A solution of **13** (0.06 g, 0.33 mmol) in dry CH_3CN (10 mL) was added to a suspension of K_2CO_3 (0.15 g, 1.08 mmol) in the same solvent (10 mL) and the mixture was refluxed for 2 h, after which allyl iodide (0.12 mL, 1.35 mmol) was added at once. Refluxing was maintained for further 2 h and next the reaction was cooled down to r.t. and diluted with water (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic layers were collected, dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. Compound **14** (0.05 g, 0.21 mmol) was obtained as a colorless oil after flash column chromatography purification (hexanes–EtOAc 9.5 : 0.5) isolating it as a colorless oil. Yield: 64%. $[\alpha]_D^{20} = -26.6$ (c = 1.0, CH_2Cl_2). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.82 (d, 3H, J = 6.7 Hz, CH_3CH), 2.12 (s, 3H, CH_3N), 2.70 (dd, 1H, J = 13.7, 7.6 Hz, CH$_a$H$_b$N), 2.76–2.95 (m, 1H, CHCH$_3$), 3.10 (dd, 1H, J = 13.7, 5.0 Hz, CH$_a$H$_b$N), 3.37 (d, 1H, J = 9.8 Hz, CHN), 4.98–5.22 (m, 4H, 2 × CH_2=CH + CH_2=CH), 5.70–6.00 (m, 2H, CH$_2$=CH + CH$_2$=CH), 7.12–7.22 (m, 2H, C$_{arom}$–H), 7.23–7.42 (m, 3H, C$_{arom}$–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 17.7 (*C*H$_3$CH), 37.8 (CH_3N), 39.1 (*C*HCH$_3$), 56.8 (CH_2N), 72.4 (CHN), 112.9 (*C*H$_2$=CH), 116.7 (*C*H$_2$=CH), 126.9, 127.7, 129.3 (C$_{arom}$–H), 136.7 (*C*$_{arom}$–C), 143.4 (CH$_2$=*C*H), 136.7 (CH$_2$=*C*H). MS (CI) [*m*/*z* (rel. abundance)]: 160 (M$^+$ − C_4H_8, 90), 125 (5), 117 (13), 84 (100), 71 (19), 57 (21). HRMS: *m*/*z* calculated for [$C_{11}H_{14}N$]$^+$: 160.1126 (M$^+$ − C_4H_8); found: 160.1134.

(2*S*,3*S*)-1,3-Dimethyl-2-phenyl-1,2,3,6-tetrahydropyridine (15)

HCl concd. (0.1 mL) was added to a cooled (0 °C) solution of **14** (0.08 g, 0.37 mmol) in Et_2O (5 mL) and the mixture was stirred at this temperature for 30 minutes after which the solvent was removed under reduced pressure obtaining the corresponding amine hydrochloride. A solution of this adduct and second generation Grubbs catalyst (14 mg, 5 mol%) in dry CH_2Cl_2 (30 mL) was refluxed for 1 h. Next, the mixture was warmed and basified carefully with NaOH 4 M until pH = 12. The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic layers were collected, dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. Piperidine **14** (0.05 g, 0.26 mmol) was obtained as a colorless oil after flash column chromatography purification (EtOAc). Yield: 70%. $[\alpha]_D^{20} = -98.5$ (c = 1.0, CH_2Cl_2). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.75 (d, 3H, J = 7.0 Hz, CH_3CH), 2.00 (s, 3H, CH_3N), 2.40–2.60 (m, 1H, CHCH$_3$), 2.68 (d, 1H, J = 8.9 Hz, CHN), 2.79–2.92 (m, 1H, CH$_a$H$_b$N), 3.30–3.44 (m, 1H, CH$_a$H$_b$N), 5.60–5.80 (m, 2H, CHCH$_2$N + CHCHCH$_3$), 7.20–7.40 (m, 5H, C$_{arom}$–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 18.4 (*C*H$_3$CH), 38.6 (CH_3N), 43.7 (*C*HCH$_3$), 55.9 (CH_2N), 74.0 (CHN), 123.8 (*C*HCHCH$_3$), 127.2 (*C*HCH$_2$N), 128.3, 128.6, 131.7 (C$_{arom}$–H), 142.2 (*C*$_{arom}$–C). MS (EI) [*m*/*z* (rel. abundance)]: 187 (M$^+$, 27), 172 (11), 168 (7), 120 (29), 118 (100), 108 (6), 91 (9), 77 (6), 68 (8). HRMS: *m*/*z* calculated for [$C_{13}H_{17}N$]$^+$: 187.1361 (M$^+$); found: 187.1361.

(2*S*,3*S*)-1,3-Dimethyl-2-phenylpiperidine (11)

A approach: LAH (0.05 g, 1.30 mol) was added to a cooled (0 °C) solution of **10** (0.05 g, 0.26 mmol) in Et_2O (10 mL). The mixture was stirred for 90 minutes at this temperature, after which H_2O (10 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic layers were collected, dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. Piperidine **11** (0.04 g, 0.18 mmol) was obtained as a colorless oil after flash column chromatography purification (hexanes–EtOAc 1 : 9). Yield: 70%. The ee was determined by HPLC using a Chiralcel OD column, (*n*-hexane); flow rate 0.50 mL min^{-1}; τ_{major} (2*S*,3*S*) isomer = 11.72 min; τ_{minor} (2*R*,3*R*) isomer = 10.48 min (98% ee). $[\alpha]_D^{20} = -99.6$ (c = 1.0, CH_2Cl_2).

B approach: A solution of the piperidine **15** (0.04 g, 0.23 mmol) in EtOAc (10 mL) was stirred in the presence of PtO_2 (10 mg, 10 mol%) under a H_2 atmosphere (balloon) at r.t. for 90 minutes. Next, the mixture was filtered and the solvent was removed under reduced pressure. Compound **11** (0.04 g, 0.21 mmol) was obtained as a colorless oil after flash column chromatography purification (hexanes–EtOAc 1 : 9). Yield: 90%. The ee was determined by HPLC using a Chiralcel OD column, (*n*-hexane); flow rate 0.50 mL min^{-1}; τ_{major} (2*S*,3*S*) isomer = 11.72 min; τ_{minor} (2*R*,3*R*) isomer = 10.48 min (98% ee). $[\alpha]_D^{20} = -105.4$ (c = 0.5, CH_2Cl_2).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.56 (d, 3H, J = 6.7 Hz, CH_3CH), 1.00–1.19 (m, 1H, CH$_a$H$_b$CH), 1.62–1.89 (m, 4H, CH$_a$H$_b$CH + CH_2CH$_2$N + CHCH$_3$), 1.93 (s, 3H, CH_3N), 2.02–2.17 (m, 1H, CH$_a$H$_b$N), 2.34 (d, 1H, J = 9.7 Hz, CHN), 2.95–3.08 (m, 1H, CH$_a$H$_b$N), 7.10–7.50 (m, 5H, C$_{arom}$–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 19.4 (*C*H$_3$CH), 25.7 (*C*H$_2$CH$_2$N), 33.7 (*C*H$_2$CH), 37.8 (*C*HCH$_3$), 44.8 (CH_3N), 57.5 (CH_2N), 78.0 (CHN), 126.9, 128.2, 128.2 (C$_{arom}$–H), 143.0 (*C*$_{arom}$–C). MS (EI) [*m*/*z* (rel. abundance)]: 189 (M$^+$, 27), 174 (16), 146 (41), 132 (23), 118 (100), 112 (80), 91

(26), 77 (7), 65 (3). HRMS: *m*/*z* calculated for $[C_{13}H_{19}N]^+$: 189.1517 (M^+); found: 189.1523.

(4*S*,5*S*,*E*)-Ethyl 4-methyl-5-methylamino-5-phenylpent-2-enoate (16)

Cerium ammonium nitrate (3.68 g, 6.71 mmol) and H_2SO_4 (100 μL) were added to a cooled (0 °C) solution of **8** (0.79 g, 2.24 mmol) in a mixture of CH_3CN–H_2O 3 : 1 (40 mL) and it was stirred for 90 minutes at this temperature, after which NaOH 4 M (10 mL) was added in order to basify it. After stirring the biphasic mixture at r.t. for a further 2 h, it was extracted with EtOAc (3 × 15 mL). The combined organic layers were collected, dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. Pure compound **16** (0.51 g, 2.06 mmol) was obtained as a yellowish oil, without any purification. Yield: 93%. $[\alpha]_D^{20} = -103.6$ (c = 1.0, CH_2Cl_2). IR (neat): 1714 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.82 (d, 3H, J = 6.8 Hz, CH_3CH), 1.29 (*t*, 3H, J = 7.1 Hz, CH_3CH$_2$), 1.50–1.58 (bs, 1H, NH), 2.17 (s, 3H, CH_3N), 2.45–2.62 (m, 1H, C*H*CH$_3$), 3.29 (d, 1H, J = 8.6 Hz, CHN), 4.20 (q, 2H, J = 7.1 Hz, CH_2), 5.91 (d, 1H, J = 15.6 Hz, CHCO), 6.91 (dd, 1H, J = 9.1, 15.6 Hz, C*H*=CHCO), 7.20–7.38 (m, 5H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.2 (*C*H$_3$CH), 17.2 (*C*H$_3$CH$_2$), 34.6 (CH$_3$N), 43.9 (*C*HCH$_3$), 60.3 (CH$_2$), 69.8 (CHN), 122.2 (*C*HCO), 127.3, 128.0, 128.3 (C_{arom}–H), 141.4 (C_{arom}–C), 151.8 (*C*H=CHCO), 166.5 (CO). MS (CI) [*m*/*z* (rel. abundance)]: 248 [(M + H)$^+$, 20], 217 (5), 202 (4), 143 (22), 120 (100), 101 (2). HRMS: *m*/*z* calculated for $[C_{15}H_{22}NO_2]^+$: 248.1651 [(M + H)$^+$]; found: 248.1649.

(4*S*,5*S*,*E*)-Ethyl 4-methyl-5-(*N*-methylbutyramido)-5-phenylpent-2-enoate (17a)

Butyric anhydride (0.10 mL, 0.64 mmol) was added to a solution of **16** (0.13 g, 0.53 mmol) and DMAP (3.3 mg, 0.02 mmol) in dry CH_2Cl_2 (10 mL) at r.t. After stirring at this temperature for 2 h, water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were collected, dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. Compound **17a** (0.17 g, 0.52 mmol) was obtained as a colorless oil after flash column chromatography purification (hexanes–EtOAc 7 : 3). Yield: 98%. $[\alpha]_D^{20} = -149.4$ (c = 1.0, CH_2Cl_2). IR (neat): 1637 (C=O), 1718 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (8 : 1 rotamer ratio; * indicates minor rotamer signals) 0.88 (t, 3H, J = 7.4 Hz, CH_3CH$_2$CH$_2$), 0.95* (t, 3H, J = 7.4 Hz, CH_3CH$_2$CH$_2$), 1.01 (d, 3H, J = 6.6 Hz, CH_3CH), 1.26 (t, 3H, J = 7.1 Hz, CH_3CH$_2$O), 1.50–1.72 (m, 2H, CH_2CH$_2$CO), 2.10–2.29 (m, 2H, CH$_2$CO), 2.30–2.37* (m, 2H, CH$_2$CO), 2.64, 2.70* (s, 3H, CH$_3$N), 3.00–3.24 (m, 1H, C*H*CH$_3$), 4.15 (q, 2H, J = 7.1 Hz, CH$_2$O), 5.83 (d, 1H, J = 11.4 Hz, CHN), 5.89 (d, 1H, J = 15.6 Hz, CHCO), 6.87 (dd, 1H, J = 9.2, 15.6 Hz, C*H*=CHCO), 7.19–7.44 (m, 5H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (8 : 1 rotamer ratio; * indicates minor rotamer signals) 13.6*, 13.8 (*C*H$_3$CH$_2$CH$_2$), 14.1*, 14.2 (*C*H$_3$CH), 17.8*, 18.0 (*C*H$_3$CH$_2$O), 18.3*, 18.5 (*C*H$_2$CH$_2$CO), 28.0*, 29.7 (CH$_3$N), 35.7, 35.9* (*C*H$_2$CO), 36.8, 36.9* (*C*HCH$_3$), 59.3 (CHN), 60.3, 60.5* (O*C*H$_2$CH$_3$), 67.0* (CHN), 121.6, 122.4* (*C*HCO), 127.7, 128.0*, 128.6, 128.9* (C_{arom}–H), 137.2*, 137.6 (C_{arom}–C), 149.2*, 150.7 (*C*H=CHCO), 165.9*, 166.2 (COO), 172.6*, 173.2 (CON). MS (CI) [*m*/*z* (rel. abundance)]: 318 [(M + H)$^+$, 71], 272 (22), 245 (20), 217 (100), 202 (38), 190 (97), 171 (11), 143 (13), 120 (44). HRMS: *m*/*z* calculated for $[C_{19}H_{28}NO_3]^+$: 318.2076 [(M + H)$^+$]; found: 318.2069.

(4*S*,5*S*,*E*)-Ethyl 4-methyl-5-(*N*-methylacetamido)-5-phenylpent-2-enoate (17b)

Ac_2O (0.24 mL, 0.23 mmol) was added to a solution of **16** (0.51 g, 2.06 mmol) and DMAP (13 mg, 0.1 mmol) in dry CH_2Cl_2 (10 mL) at r.t. After stirring at this temperature for 2 h, water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were collected, dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. Compound **17b** (0.53 g, 1.84 mmol) was obtained as a colorless oil after flash column chromatography purification (hexanes–EtOAc 6 : 4). Yield: 89%. $[\alpha]_D^{20} = -158.3$ (c = 1.0, CH_2Cl_2). IR (neat): 1645 (C=O), 1716 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (5 : 1 rotamer ratio; * indicates minor rotamer signals) 0.99 (d, 3H, J = 6.6 Hz, CH_3CH), 1.25 (t, 3H, J = 7.1 Hz, CH_3CH$_2$), 1.96 (s, 3H, CH$_3$CO), 2.03* (s, 3H, CH$_3$CO), 2.64 (s, 3H, CH$_3$N), 2.67* (s, 3H, CH$_3$N), 3.00–3.30 (m, 1H, C*H*CH$_3$), 4.15 (q, 2H, J = 7.1 Hz, CH$_2$), 5.77 (d, 1H, J = 11.4 Hz, CHN), 5.89 (d, 1H, J = 15.6 Hz, CHCO), 5.92* (d, 1H, J = 15.5 Hz, CHCO), 6.87 (dd, 1H, J = 9.1, 15.6 Hz, C*H*=CHCO), 7.17–7.42 (m, 5H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (5 : 1 rotamer ratio; * indicates minor rotamer signals) 14.2 (*C*H$_3$CH), 17.9*, 18.0 (*C*H$_3$CH$_2$O), 22.0, 22.2* (*C*H$_3$CO), 27.8*, 30.4 (CH$_3$N), 36.7, 37.3* (*C*HCH$_3$), 59.4, 66.2* (CHN), 60.3, 60.5* (CH$_2$), 121.6, 122.4* (*C*HCO), 127.8, 127.9*, 128.3*, 128.5, 128.6, 128.9* (C_{arom}–H), 137.0*, 137.5 (C_{arom}–C), 149.0*, 150.5 (*C*H=CHCO), 165.9*, 166.2 (COO), 170.1*, 170.8 (CON). MS (CI) [*m*/*z* (rel. abundance)]: 290 [(M + H)$^+$, 31], 245 (20), 217 (100), 202 (44), 171 (15), 162 (64), 143 (15), 120 (27), 74 (3). HRMS: *m*/*z* calculated for $[C_{17}H_{24}NO_3]^+$: 290.1756 [(M + H)$^+$]; found: 290.1767.

(4*S*,5*S*,*E*)-Ethyl 5-(2-bromo-*N*-methylbutyramido)-4-methyl-5-phenylpent-2-enoate (18a)

DCC (1.23 g, 5.94 mmol) and 2-bromobutyric acid (0.63 mL, 5.94 mmol) were added to a solution of **16** (0.16 g, 0.66 mmol) and DMAP (4 mg, 0.03 mmol) in dry CH_2Cl_2 (10 mL) at r.t. After stirring at this temperature for 90 minutes, water (10 mL) was added and the mixture was filtered and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (10 mL) and H_2O (10 mL), collected, dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. Compound **18a** (0.26 g, 0.65 mmol) was obtained as a yellowish oil after flash column chromatography purification (hexanes–EtOAc 9 : 1). Yield: 98% (dr: >95 : 5). IR (neat): 1649 (C=O), 1718 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (20 : 1 rotamer ratio; * indicates minor rotamer signals) 0.94 (t, 3H, J = 7.3 Hz, CH_3CH$_2$CH), 1.10 (d, 3H, J = 6.5 Hz, CH_3CH), 1.28 (t, 3H, J = 7.1 Hz, CH_3CH$_2$O), 1.95–2.06 (m, 1H, CH_aH$_b$CH), 2.19–2.31 (m, 1H, CH$_a$H$_b$CH), 2.72 (s, 3H, CH$_3$N), 2.95* (s, 3H, CH$_3$N), 3.10–3.25 (m, 1H, C*H*CH$_3$), 4.10–4.23 (m, 3H, CHBr + OCH$_2$), 5.85 (d,

1H, $J = 11.4$ Hz, CHN), 5.93 (d, 1H, $J = 15.6$ Hz, CHCOO), 6.89 (dd, 1H, $J = 15.6$, 9.3 Hz, C*H*=CHCO), 7.26–7.42 (m, 5H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.1 (*C*H_3CH$_2$CH), 14.2 (*C*H_3CH), 18.0 (*C*H_3CH$_2$O), 28.4 (*C*H_2CH), 29.6 (CH_3N), 36.6 (*C*HCH$_3$), 45.4 (CHBr), 60.0 (CHN), 60.3 (CH_2O), 121.8 (*C*HCOO), 128.0, 128.6, 128.7 (C_{arom}–H), 136.5 (C_{arom}–C), 150.3 (*C*H=CHCO), 166.0 (COO), 168.8 (CON). MS (CI) [*m*/*z* (rel. abundance)]: 396 [(M + H)$^+$, 11], 350 (13), 316 (15), 270 (42), 245 (16), 217 (100), 202 (33), 171 (11), 143 (13), 120 (17). HRMS: *m*/*z* calculated for [$C_{19}H_{27}NO_3Br$]$^+$: 396.1174 [(M + H)$^+$]; found: 396.1183.

(4*S*,5*S*,*E*)-Ethyl 5-(2-bromo-*N*-methylacetamido)-4-methyl-5-phenylpent-2-enoate (18b)

DCC (1.19 g, 5.79 mmol) and 2-bromoacetic acid (0.42 mL, 5.79 mmol) were added to a solution of **16** (0.16 g, 0.64 mmol) and DMAP (4 mg, 0.03 mmol) in dry CH_2Cl_2 (10 mL) at r.t. After stirring at this temperature for 90 minutes, water (10 mL) was added and the mixture was filtered and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (10 mL) and H_2O (10 mL), collected, dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. Compound **18b** (0.20 g, 0.55 mmol) was obtained as a yellowish oil after flash column chromatography purification (hexanes–EtOAc 7 : 3). Yield: 86%. $[\alpha]_D^{20} = -145.2$ ($c = 1.0$, CH_2Cl_2). IR (neat): 1651 (C=O), 1716 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (8 : 1 rotamer ratio; * indicates minor rotamer signals) 1.04 (d, 3H, $J = 6.6$ Hz, C*H*$_3$CH), 1.27 (t, 3H, $J = 7.1$ Hz, C*H*$_3$CH$_2$), 2.75 (s, 3H, CH_3N), 2.78* (s, 3H, CH_3N), 3.09–3.30 (m, 1H, C*H*CH$_3$), 3.73 (d, 1H, $J = 10.6$ Hz, C*H*$_a$H$_b$Br), 3.78 (d, 1H, $J = 10.6$ Hz, CH$_a$*H*$_b$Br), 4.17 (q, 2H, $J = 7.1$ Hz, OC*H*$_2$CH$_3$), 5.70 (d, 1H, $J =$ 11.4 Hz, CHN), 5.93 (d, 1H, $J = 15.6$ Hz, CHCO), 6.88 (dd, 1H, $J = 15.6$, 9.2 Hz, C*H*=CHCO), 6.98* (dd, 1H, $J = 15.8$, 8.6 Hz, C*H*=CHCO), 7.26–7.42 (m, 5H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.3 (*C*H_3CH), 18.0 (*C*H_3CH$_2$), 26.5 (CH_2Br), 30.4 (CH_3N), 36.8 (*C*HCH$_3$), 60.1 (CHN), 60.4 (O*C*H$_2$CH$_3$), 122.2 (*C*HCO), 128.1, 128.6, 128.8 (C_{arom}–H), 136.7 (C_{arom}–C), 149.6 (*C*H=CHCO), 166.0 (COO), 166.8 (CON). MS (CI) [*m*/*z* (rel. abundance)]: 368 [(M + H)$^+$, 12], 324 (24), 288 (29), 245 (19), 242 (58), 217 (100), 202 (11), 171 (30), 143 (15), 120 (13). HRMS: *m*/*z* calculated for [$C_{17}H_{23}NO_3Br$]$^+$: 368.0869 [(M + H)$^+$]; found: 368.0861.

(3*S*,4*R*,5*S*,6*S*)-4-Ethoxycarbonylmethyl-3-ethyl-1,5-dimethyl-6-phenyl-piperidin-2-one (19/19′)

Compound **18a** (0.08 g, 0.19 mmol) was slowly added to a cooled (−105 °C) suspension of LiCl (0.02 g, 0.57 mmol) in THF (10 mL). *n*-BuLi 1.1 M (0.19 mL, 0.21 mmol) was then added dropwise and the mixture stirred for 15 min at this temperature. H_2O was added and the reaction was warmed to r.t. and extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Piperidinone **19**/**19′** (0.03 g, 0.10 mmol) was obtained as a colorless oil after flash column chromatography purification. Yield: 54% (dr: 92 : 8). $[\alpha]_D^{20} = +41.3$ ($c = 1.0$, CH_2Cl_2). IR (neat): 1637 (C=O), 1734 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (92 : 8 diastereoisomer ratio; * indicates minor diastereoisomer signals) 0.85* (d, 3H, $J = 6.4$ Hz, C*H*$_3$CH), 0.97 (d, 3H, $J = 6.9$ Hz, C*H*$_3$CH), 1.02 (t, 3H, $J = 7.4$ Hz, C*H*$_3$CH$_2$CH), 1.15 (t, 3H, $J = 7.1$ Hz, C*H*$_3$CH$_2$O), 1.22* (t, 3H, $J = 7.1$ Hz, C*H*$_3$CH$_2$O), 1.75–1.99 (m, 2H, CH$_3$C*H*$_2$CH), 2.13–2.22 (m, 1H, C*H*CH$_3$), 2.23–2.40 (m, 4H, C*H*$_2$CO + CHCHCON), 2.58* (s, 3H, CH_3N), 2.72 (s, 3H, CH_3N), 3.64–3.74* (m, 1H, C*H*$_a$H$_b$O), 3.78* (d, 1H, $J = 9.7$ Hz, CHN), 4.00 (d, 1H, $J = 6.8$ Hz, CHN), 4.02–4.10 (m, 2H, CH_2O), 4.11–4.19* (m, 1H, C*H*$_a$H$_b$O), 7.08–7.15 (m, 2H, C_{arom}–H), 7.15–7.19* (m, 2H, C_{arom}–H), 7.25–7.31* (m, 3H, C_{arom}–H), 7.32–7.39 (m, 3H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (92 : 8 diastereoisomer ratio; * indicates minor diastereoisomer signals) 11.5, 13.5* (*C*H_3CH$_2$CH), 14.1, 14.2* (*C*H_3CH$_2$O), 14.7, 15.8* (*C*H_3CH), 21.3*, 23.7 (*C*H$_2$CHCO), 32.9*, 33.3 (*C*HCH$_2$CO), 34.1 (*C*H_3N), 34.5 (*C*H$_2$CO), 35.5* (*C*H_3N), 35.6 (*C*HCH$_3$), 37.4* (*C*H$_2$CO), 38.2* (*C*HCH$_3$), 46.4 (*C*HCO), 60.5, 60.7* (O*C*H$_2$CH$_3$), 68.8, 71.6* (CHN), 126.8, 127.6*, 127.8, 127.9*, 128.7, 128.8* (C_{arom}–H), 140.7, 141.2* (C_{arom}–C), 172.2 (COO), 172.4, 173.1* (CON). MS (CI) [*m*/*z* (rel. abundance)]: 318 [(M + H)$^+$, 100], 289 (5), 272 (7), 202 (5), 147 (5). HRMS: *m*/*z* calculated for [$C_{19}H_{28}NO_3$]$^+$: 318.2069 [(M + H)$^+$]; found: 318.2058.

(4*S*,5*S*,*E*)-Ethyl 4-methyl-5-(*N*-methyl-2-phenylsulfonylacetamido)-5-phenylpent-2-enoate (20)

Sodium benzenesulfinate (0.04 g, 0.23 mmol) was added to a solution of **18b** (0.09 g, 0.23 mmol) in DMF (10 mL) at r.t. for a period of 30 minutes. After stirring at this temperature for 1 h, H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (10 mL) and H_2O (10 mL), collected, dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. Compound **20** (0.09 g, 0.20 mmol) was obtained as a yellowish oil after flash column chromatography purification (hexanes–EtOAc 6 : 4). Yield: 86%. $[\alpha]_D^{20} = -104.0$ ($c = 1.0$, CH_2Cl_2). IR (neat): 1152 (SO_2), 1318 (SO_2), 1654 (C=O), 1720 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (13 : 1 rotamer ratio; * indicates minor rotamer signals) 1.00 (d, 3H, $J = 6.5$ Hz, C*H*$_3$CH), 1.06* (d, 3H, $J = 6.6$ Hz, C*H*$_3$CH), 1.27 (t, 3H, $J = 7.1$ Hz, C*H*$_3$CH$_2$), 2.77* (s, 3H, CH_3N), 2.88 (s, 3H, CH_3N), 3.07–3.27 (m, 1H, C*H*CH$_3$), 4.02–4.25 (m, 4H, CH_2O + CH_2S), 5.63 (d, 1H, $J = 11.5$ Hz, CHN), 5.99 (d, 1H, $J = 15.6$ Hz, CHCO), 6.89 (dd, 1H, $J = 15.6$, 9.1 Hz, C*H*=CHCO), 7.12 (dd, 1H, $J = 15.6$, 9.0 Hz, C*H*=CHCO), 7.21–7.46 (m, 5H, C_{arom}–H), 7.47–7.60 (m, 2H, C_{arom}–H), 7.60–7.73 (m, 1H, C_{arom}–H), 7.78–7.91 (m, 2H, C_{arom}–H), 7.91–8.01* (m, 2H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.2 (*C*H_3CH), 18.0 (*C*H_3CH$_2$O), 31.1 (CH_3N), 36.6 (*C*HCH$_3$), 60.1 (CH_2S), 60.4 (CH_2O), 60.5 (CHN), 122.4 (*C*HCOO), 128.2, 128.5, 128.7, 128.8, 129.0, 134.1 (C_{arom}–H), 136.7, 138.5 (C_{arom}–C), 149.4 (*C*H=CHCO), 161.7 (COO), 166.2 (CON). MS (CI) [*m*/*z* (rel. abundance)]: 430 [(M + H)$^+$, 100], 384 (9), 365 (26), 288 (14), 278 (9), 200 (2). HRMS: *m*/*z* calculated for [$C_{23}H_{28}NO_5S$]$^+$: 430.1707 [(M + H)$^+$]; found: 430.1688.

(3*S*,4*R*,5*S*,6*S*)-4-Ethoxycarbonylmethyl-1,5-dimethyl-6-phenyl-3-phenylsulfonylpiperidin-2-one (21)

A solution of compound **20** (0.07 g, 0.16 mmol) in dry THF (5 mL) was added to a cooled (−40 °C) solution of sodium hydride (0.19 g, 0.80 mmol) in the same solvent. The mixture was stirred for 3 h at this temperature, after which H_2O (10 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3 × 15 mL) and the combined organic layers were collected, dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. Piperidinone **21** (0.05 g, 0.12 mmol) was obtained as a colorless oil after flash column chromatography purification (hexanes–EtOAc 1 : 1). Yield: 81% (dr: 92 : 8). $[\alpha]_D^{20} = -8.0$ ($c = 1.0$, CH_2Cl_2). IR (neat): 1146 (SO_2), 1306 (SO_2), 1650 (C═O), 1728 (C═O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (92 : 8 diastereoisomer ratio; * indicates minor diastereoisomer signals) 0.92 (d, 3H, J = 6.7 Hz, CH_3CH), 1.26 (t, 3H, J = 7.3 Hz, CH_3CH$_2$), 2.13–2.43 (m, 1H, CH_aH$_b$CO), 2.66 (s, 3H, CH_3N), 2.73 (dd, 1H, J = 16.8, 3.8 Hz, CH_aH$_b$CO), 2.78–2.92 (m, 1H, C*H*CH$_3$), 3.26–3.42 (m, 1H, C*H*CH$_2$), 3.89 (d, 1H, J = 10.3 Hz, CHN), 4.09–4.18 (m, 2H, OCH_2), 4.30 (d, 1H, J = 1.8 Hz, CHS), 7.29–7.49 (m, 5H, C_{arom}–H), 7.50–7.72 (m, 3H, C_{arom}–H), 7.92–7.97* (m, 2H, C_{arom}–H), 7.97–8.07 (m, 2H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (92 : 8 diastereoisomer ratio; * indicates minor diastereoisomer signals) 14.1 (*C*H$_3$CH$_2$), 15.4 (*C*H$_3$CH), 31.2 (*C*H$_2$CO), 33.6 (CH_3N), 33.7 (*C*HCH$_2$), 33.8* (*C*H$_2$CO), 35.7 (*C*HCH$_3$), 36.9* (CH_3N), 38.2* (*C*HCH$_3$), 61.0 (CH_2O), 68.3, 69.0* (CHN), 70.3, 72.1 (CHS), 127.9, 128.3, 128.8, 129.0, 133.8 (C_{arom}–H), 139.1, 140.4 (C_{arom}–C), 161.7 (COO), 171.3, 172.6* (CON). MS (CI) [*m*/*z* (rel. abundance)]: 430 [(M + H)$^+$, 100], 384 (6), 365 (26), 288 (14), 278 (9). HRMS: *m*/*z* calculated for $[C_{23}H_{28}NO_5S]^+$: 430.1703 [(M + H)$^+$]; found: 430.1688.

(4*R*,5*S*,6*S*)-4-Methoxycarbonylmethyl-1,5-dimethyl-6-phenylpiperidin-2-one (22)

Mg (0.08 g, 0.33 mmol) was added to a cooled (0 °C) solution of compound **21** (0.10 g, 0.22 mmol) in MeOH (3 mL). The mixture was stirred for 5 h at r.t., after which the mixture was filtered and the solvent was removed under reduced pressure. Piperidinone **22** (0.05 g, 0.18 mmol) was obtained as a colorless oil after flash column chromatography purification (hexanes–EtOAc 1 : 1). Yield: 80% (dr: 92 : 8). $[\alpha]_D^{20}$ = +27.1 (c = 1.0, CH_2Cl_2). IR (neat): 1641 (C═O), 1734 (C═O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (92 : 8 diastereoisomer ratio; * indicates minor diastereoisomer signals) 0.86* (d, 3H, J = 6.5 Hz, CH_3CH), 1.07 (d, 3H, J = 7.0 Hz, CH_3CH), 1.96–2.12 (m, 1H, C*H*CH$_3$), 2.14–2.32 (m, 3H, CH_2COO + CH_aH$_b$CON), 2.33–2.49 (m, 1H, C*H*CH$_2$), 2.55–2.72 (m, 1H, CH_aH$_b$CON), 2.81 (s, 3H, CH_3N), 3.58 (s, 3H, CH_3O), 3.67* (s, 3H, CH_3O), 3.86 (d, 3H, J = 10.0 Hz, CHN), 4.20 (d, 3H, J = 3.8 Hz, CHN), 7.05–7.15 (m, 2H, C_{arom}–H), 7.15–7.21* (m, 2H, C_{arom}–H), 7.23–7.45 (m, 3H, C_{arom}–H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (92 : 8 diastereoisomer ratio; * indicates minor diastereoisomer signals) 13.6, 15.4* (*C*H$_3$CH), 28.7, 32.9* (*C*HCH$_2$), 34.3 (CH_3N), 34.6 (*C*H$_2$CON), 34.7* (CH_3N), 36.4 (*C*H$_2$COO), 37.6* (*C*H$_2$CON), 38.4* (*C*H$_2$COO), 38.6, 42.3* (*C*HCH$_3$), 51.6, 51.8* (CH_3O), 69.8, 71.2* (CHN), 126.4, 127.7, 128.1*, 128.9 (C_{arom}–H), 140.5, 140.8* (C_{arom}–C), 169.5 (CON), 172.2 (COO). MS (CI) [*m*/*z* (rel. abundance)]: 276 [(M + H)$^+$, 100], 244 (17), 147 (7), 118 (4). HRMS: *m*/*z* calculated for $[C_{16}H_{22}NO_3]^+$: 276.1599 [(M + H)$^+$]; found: 276.1611.

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