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Synthesis of Enantiomerically Pure 3-Amino-2-methylenealkanoates (Aza-Morita–Baylis–Hillman Adducts) Mediated by *Cinchona* Alkaloids

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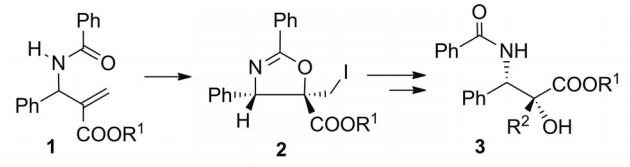
3-Substituted (*Z*)-2-(bromomethyl)propenoates reacted with (*S*)-1-(4-methoxyphenyl)ethylamine in the presence of a stoichiometric amount of quinidine to yield (*R*)-3-[(*tert*-butoxycarbonyl)amino]-2-methylenealkanoates (aza-Morita–Baylis–Hillman adducts) in enantiomerically pure form.

Introduction

3-Amino-2-methylenealkanoic acids have become an attractive class of organic compounds displaying high functional density. In recent years they have also gained popularity as substrates and building blocks in synthesis. The *S* enantiomers have recently been prepared by a multistep synthesis[1] and incorporated into peptides owing to the conformational restriction arising from the conjugated double bond, but stable secondary structures were not evidenced either in solution or in the solid state.[2] Moreover, 3-amino-2-methylenealkanoic acids and their derivatives are key precursors to many natural products that have been reported to display interesting biological activities.[3] Much effort has been devoted to the stereoselective synthesis of these compounds, especially by the aza-Morita–Baylis–Hillman (AMBH) reaction.[4] However, despite recent attempts, most of these routes suffer from several drawbacks such as moderate enantioselectivity and yields, poor substrate generality, expensive catalysts and the poor availability of acrylates and imines. Finally, they cannot be readily scaled up to provide a really useful amount of product.[5] This is also true for the few alternative asymmetric strategies to these compounds that do not exploit the AMBH methodology.[6]

Results and Discussion

We have previously reported a procedure for the preparation of racemic 3-acylamino-2-methylenealkanoates **1** starting from the *N*-acylcarbamates of MBH adducts,[7] which allowed analogues of bioactive 3-amino-2-hydroxy acids **3** to be obtained by totally stereoselective cyclofunctionalization reactions (Scheme 1).[8]



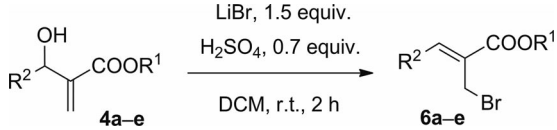
R^1 = alkyl; **a**: $R^2 = CH_3$ **b**: $R^2 = CH_2OH$ **c**: $R^2 = CH_2NH_2$ **d**: $R^2 = CH_2F$

Scheme 1. Stereoselective iodocyclization of 3-acylamino-2-methylenealkanoates.

Owing to the interest in compounds such as **3**, which are isosteres of the C-13 side-chain of paclitaxel (Taxol®),[8] to complement our work we herein disclose the preparation of enantiopure *N*-protected 3-amino-2-methylenealkanoates.

Treatment of derivatives of MBH adducts **4** with an amine converts the hydroxy group into a leaving group, giving mainly 2-aminomethyl derivatives by an S_N2' pathway.[9] Thus, we devised a double S_N2' process exploiting (*S*)-1-(4-methoxyphenyl)ethylamine (**5**) as chiral inducer. First the racemic MBH adducts **4a**–**e** were treated with LiBr and H_2SO_4 to give with very high stereoselectivity[10] and in quantitative yield the corresponding (*Z*)-bromomethyl derivatives **6a**–**e** (Table 1).

Table 1. Preparation of (*Z*)-2-(bromomethyl)-2-alkenoates **6**.



Entry	R^1	R^2	Yield [%][a]
a	Me	Ph	quantitative
b	Me	4-O_2N-C_6H_4	quantitative
c	Et	4-Cl-C_6H_4	quantitative
d	Et	2-naphthyl	quantitative
e	Me	*i*Bu	90

[a] Yield of the pure isolated product, measured relative to 0.1 mol of **4a**–**e**.

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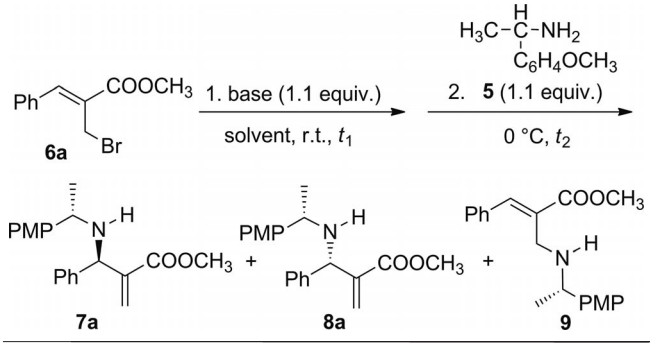
Then compound **6a** was treated first with triethylamine in various solvents, rapidly followed by **5**, to give the diastereomeric amines **7a** and **8a** in moderate yields with almost no diastereoselectivity. Moreover, the simultaneous formation of substantial amounts of the aminomethyl derivative **9** due to direct substitution at the carbon atom bearing the leaving group strongly affects the yields of the desired diastereomers **7** and **8** (Table 2, entries a–c).

Table 2. Reactions of **6a** with (*S*)-1-(4-methoxyphenyl)ethylamine (**5**) under different conditions.



Entry	Base (t_1)	Solvent (t_2)	Overall yield [%][a]	Ratio[b] **7a/8a/9**
a	Et_3N (1 min)	DCM (1 h)	88	37:35:28
b	Et_3N (1 min)	MeOH (9 h)	91	31:34:35
c	Et_3N (1 min)	DMSO (1 h)	90	17:15:68
d	Et_3N (2 h)[c]	$CHCl_3$ (2 h)	82	72:28:0
e	EPIP[d] (5 h)	DCM (1.5 h)	79	66:33:1
f	TMEDA (1 h)	DCM (2 h)	73	74:24:2
g	Ph_3P (40 min)[e]	DCM (4 d)	92	83:17:0
h	3-HQD[d] (20 min)	DCM (1 h)	89	76:22:2
i	DABCO (20 min)	DCM (1 h)	91	75:24:1

[a] Yield of the pure isolated product. [b] Determined for the crude reaction mixture by ^{1}H NMR spectroscopy. [c] Reflux temperature was required for the intermediate formation. [d] Abbreviations: EPIP = *N*-ethylpiperidine, 3-HQD = 3-quinuclidinol. [e] Et_3N (1 equiv.) was also added.

This side-reaction was especially significant when DMSO was used as solvent and it is worth mentioning that this solvent also promotes the slow rearrangement of diastereomers **7** and **8** into the aminomethyl derivative **9** (see the Supporting Information for the necessary cautions).

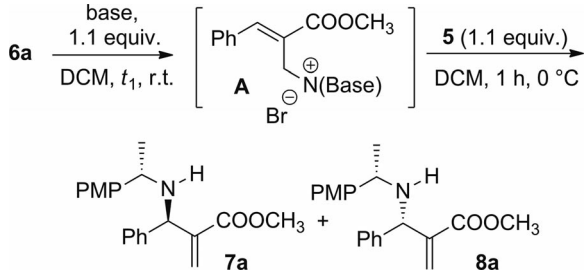
Thus, with the aim of obtaining compounds **7** and **8** exclusively by an S_N2' process, we carried out the reaction on the corresponding quaternary ammonium salt.

In fact, when the reaction mixture was heated at reflux for 2 h in chloroform before adding **5**, or bases more nucleophilic than Et_3N were used, we observed increased diastereoselectivity together with an almost negligible formation of **9** (Table 2, entries d–i).[11] Note that all the reaction mixtures were easily separable by silica gel chromatography. The configurations reported for **7a** and **8a** were assigned by conversion into derivatives, the configurations of which were determined by ^{1}H NMR spectroscopy and confirmed by comparison of the optical rotation of the final product **10a** with literature data (see the Supporting Information).

We envisioned that higher levels of diastereoselectivity could be obtained by a double asymmetric induction and for this purpose the latter S_N2' reaction was performed with the quaternary ammonium salt prepared starting from **6a** and tertiary chiral amines bearing an additional hydroxy group. In fact, a hydrogen bond formed with the incoming nucleophile could give rise to restriction of the conformational freedom in the transition state and consequent increased stereoselectivity.

Thus, we treated compound **6a** with quinidine, quinine, cinchonine and cinchonidine to prepare the corresponding salts **A** (see the Supporting Information). The subsequent S_N2' reaction was carried out by using either (*S*)- or (*R*)-1-(4-methoxyphenyl)ethylamine (**5**). We observed that match/mismatch effects take place and that the side-product **9** was completely suppressed (see Tables 3 and 4).

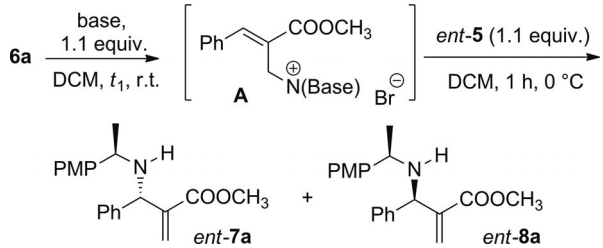
Table 3. Reactions of **(*S*)-5** with quaternary ammonium salts of *Cinchona* alkaloids obtained from **6a**.



Entry	Base (t_1 [h])	Overall yield [%][a]	Ratio[b] **7a/8a**
a	quinidine (3)	94	94:6
b	quinine (3)	85	41:59
c	cinchonine (24)[c]	90	85:15
d	cinchonidine (3)	86	65:35

[a] Yield of pure isolated products, measured relative to 1 mmol of **6a**. [b] Determined for the crude reaction mixture by ^{1}H NMR spectroscopy. [c] A 1:1 mixture of DCM/MeOH was required for the formation of quaternary ammonium salt **A**.

Table 4. Reactions of (*R*)-*ent*-**5** with quaternary ammonium salts of *Cinchona* alkaloids obtained from **6a**.



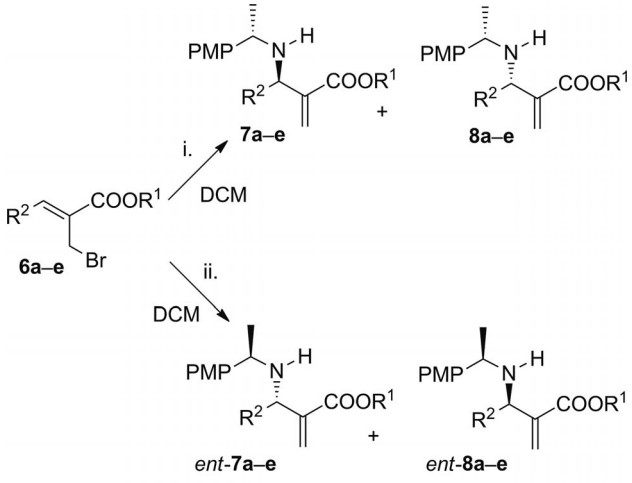
Entry	Base (t_1 [h])	Overall yield [%][a]	Ratio[b] *ent*-**7a**/*ent*-**8a**
a	quinidine (3)	89	29:71
b	quinine (3)	93	90:10
c	cinchonine (24)[c]	87	37:63
d	cinchonidine (3)	88	64:36

[a] Yield of pure isolated products, measured relative to 1 mmol of **6a**. [b] Determined for the crude reaction mixture by ^{1}H NMR spectroscopy. [c] A 1:1 mixture of DCM/MeOH was required for the formation of quaternary ammonium salt **A**.

In fact, the *Si* diastereofacial preference of **(*S*)-5** significantly increased (Table 3, entries a and c) when quinidine or cinchonine were used to generate the intermediate ammonium salt **A**. It is apparent that **(*S*)-5** and quinidine or cinchonine are well-matched pairs leading predominantly to **7a**, whereas **(*S*)-5** with quinine or cinchonidine are mismatched (Table 3, entries b and d).

On the other hand, (*R*)-*ent*-**5** displayed good *Re* diastereofacial preference when quinine was used to generate the ammonium salt **A**. Thus, (*R*)-*ent*-**5** and quinine are a well-matched pair leading to *ent*-**7a** (Table 4, entry b). Thus, either **7a** or *ent*-**7a** are easily accessible by simply exploiting the chirality of **5** or *ent*-**5** with the appropriate chiral tertiary base. In fact, by only changing the reagents, both compounds **7a** and *ent*-**7a** can be obtained pure and in high yields owing to the high stereoselectivity of the reaction and the easy separation from the minor diastereomers **8a** and *ent*-**8a** by silica gel chromatography.

Table 5. Preparation of amino derivatives **7a**–**e** and *ent*-**7a**–**e**.



Conditions i: quinidine (1.1 equiv.), 3 h, r.t., then (*S*)-**5** (1.1 equiv.), 1 h, 0 °C
Conditions ii: quinine (1.1 equiv.), 3 h, r.t., then (*R*)-*ent*-**5** (1.1 equiv.), 1 h, 0 °C

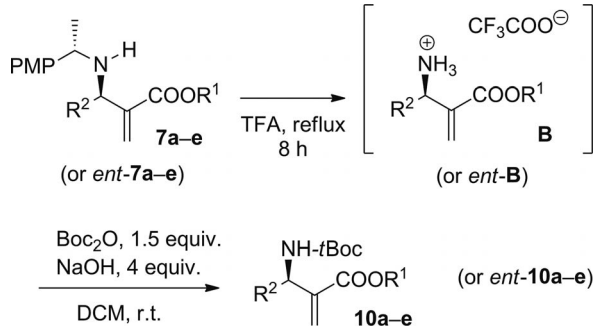
Conditions i. Entry	R^1	R^2	Yield of **7** [%][a]	Ratio[b] **7/8**
a	Me	Ph	89 (82)[c] (85)[d]	94:6 (91:9)[c]
b	Me	4-O_2N-C_6H_4	78	82:18
c	Et	4-Cl-C_6H_4	86	94:6
d	Et	2-naphthyl	89	90:10
e	Me	*i*Bu	72	85:15
Conditions ii. Entry	R^1	R^2	Yield of *ent*-**7** [%][a]	Ratio[b] *ent*-**7**/*ent*-**8**
f	Me	Ph	84 (80)[c]	90:10 (88:12)[c]
g	Me	4-O_2N-C_6H_4	81	86:14
h	Et	4-Cl-C_6H_4	89	93:7
i	Et	2-naphthyl	84	89:11
l	Me	*i*Bu	60	68:32

[a] Yield of pure isolated **7a**–**e** (or *ent*-**7a**–**e**), measured relative to 10 mmol of **6a**–**e**. [b] Determined on the crude reaction mixture by ^{1}H NMR spectroscopy. [c] Reaction with recycled quinidine or quinine. [d] Yield of the pure product from the reaction carried out with 100 mmol of **6a**.

With the optimal reaction conditions identified, a series of enantiomerically pure 3-amino-2-methylenealkanoates **7** and *ent*-**7** were synthesized to establish the generality of this methodology (Table 5). The reaction was seen to be general, offering yields of 72–89% and *dr* values ranging from 82:18 to 94:6 for reactions carried out with quinidine and (*S*)-**5** (conditions i.). On the other hand, slightly lower yields (60–89%) and *dr* values (from 68:32 to 93:7) were obtained when quinine and **(*R*)-*ent*-5** were used (conditions ii.). Moreover, all the reaction mixtures were easily purified by FC and the reactions carried out using the recovered chiral base furnished products **7a** and *ent*-**7a** with only very slight decreases in yield and stereoselectivity (entries a and f). Finally, by using conditions i., compound **7a** was prepared on a large scale (100 mmol) starting from **6a** with almost identical stereoselectivity and yield (entry a).

The chiral inducer was removed from compounds **7** and *ent*-**7** at reflux in TFA. The intermediate salts **B** were directly converted, without isolation, into the corresponding *t*Boc derivatives **10a**–**e** in good-to-excellent yields considering that the overall process involves two steps (Table 6). The configurations of compounds **10a**,**c**,**e** were confirmed by comparison with reported optical rotations, whereas the remaining ones were assigned by similarity to **10a**,**c**,**e** (see the Supporting Information).[1,6c,6d] Moreover, as evidenced by HPLC analysis, the *ee* values of the products were invariably the same or even greater than those of the chiral inducers employed (*S*)-**5** and (*R*)-*ent*-**5** (see the Supporting Information).

Table 6. Preparation of (*R*)- and (*S*)-3-[(*tert*-butoxycarbonyl)-amino]-2-methylenealkanoates **10** and *ent*-**10**.



Entry	R^1	R^2	Yield [%][a]
a	Me	Ph	85[b]
b	Me	4-O_2N-C_6H_4	72
c	Et	4-Cl-C_6H_4	80[b]
d	Et	2-naphthyl	93
e	Me	*i*Bu	63[b,c]

[a] Average yield of the pure product after isolation, measured relative to 5 mmol of **7** (or *ent*-**7**). [b] The absolute configuration was assigned by comparison of the optical rotation with a known value (see the Supporting Information). [c] Heating carried out at reflux for 72 h.

Conclusions

Starting from racemic Morita–Baylis–Hillman adducts **4** we have developed a straightforward and easily scalable

synthesis of *N*-protected 3-amino-2-methylenealkanoates **10** (aza-Morita–Baylis–Hillman adducts) in both enantiomerically pure forms simply by changing quinidine for quinine and (*R*)-*ent*-**5** for (*S*)-**5**. In addition, *Cinchona* alkaloids were recovered and used again without significant loss of yield and stereoselectivity. Reactions aimed at preparing enantiomerically pure analogues of 3-amino-2-hydroxy acids **3** from these compounds are currently underway and the results will be reported in due course. Moreover, we are carrying out a computational investigation aimed at obtaining a better insight into the mechanistic effect of the chiral tertiary base on the stereoselectivity.

Finally, with the aim of achieving results similar to those presented here, but by using an achiral and cheaper tertiary base than *Cinchona* alkaloids, further studies exploring the influence of different anions of the quaternary ammonium salts **A** on the diastereoselectivity of the S_N2' reaction are underway.

Experimental Section

General Methods: Melting points were measured with an Electrothermal IA 9000 apparatus. R_f values refer to elution on silica gel TLC-PET foils with the specified eluent. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with a Varian MR-400 spectrometer in $CDCl_3$ at 25 °C. Chemical shifts are reported in ppm relative to residual solvent signals (δ =7.26 and 77.16 ppm for ^1H and ^{13}C NMR, respectively[12]) and coupling constants (J) are given in Hz. Mass spectra were recorded using electrospray (ES) ionization. Specific rotation measurements, $[\alpha]_D^{20}$, were recorded at room temperature with a Perkin–Elmer Model 241 polarimeter at the sodium D line (concentration in g/100 mL). The enantiomeric purity of products **10a**–**e** and *ent*-**10a**–**e** was confirmed by HPLC analysis using a Hewlett–Packard 1100 chromatograph equipped with a Daicel Chiralcel® OD-H column and a diode array UV detector (210, 230 and 250 nm). The absolute configurations of some of the final products (**10a**, **10c** and **10e**) were determined by comparison of the optical rotations with literature values. The absolute configurations of the remaining final products were assigned on the basis that the same chiral tertiary base/chiral inducer couple [quinidine/(*S*)-(–)-1-(4-methoxyphenyl)ethylamine or quinine/(*R*)-(–)-1-(4-methoxyphenyl)ethylamine] always furnished good diastereoselectivities with very similar ratios of the diastereomers **7a**–**e**/**8a**–**e** or *ent*-**7a**–**e**/*ent*-**8a**–**e**, which indicates that the diastereoselective addition of the chiral inducer occurs preferentially at the same face of the double bond in the various quaternary ammonium salt intermediates. Moreover, the R_f values of **8a**–**e** (or *ent*-**8a**–**e**) are always greater than those of **7a**–**e** (or *ent*-**7a**–**e**).

Materials: Analytical-grade solvents and commercially available reagents were used as received. Anhydrous DCM was obtained by distillation over CaH_2 and stored over 4 Å molecular sieves. The petroleum ether 30–50 or 35–60 °C boiling-point fractions were used. (*S*)-(–)-1-(4-Methoxyphenyl)ethylamine was purchased from various suppliers with variable enantiomeric purities, namely with an *ee* ranging from ≥95 to ≥98.5%, whereas for (*R*)-(+)-1-(4-methoxyphenyl)ethylamine the *ee* ranged from ≥98 to ≥99%. In any case, the residual quantities of the minor enantiomer in the commercially available chiral inducers gave very small amounts of the minor enantiomer in the products **10a**–**e** (or *ent*-**10a**–**e**; see main text and below). HPLC-grade 2-propanol and *n*-hexane were used as the eluting solvents. Column chromatography was performed by using Kieselgel 60 Merck (230–400 mesh ASTM) unless specified otherwise. TLC was performed by using Fluka silica gel TLC-PET foils unless specified otherwise.

General Procedure for the Preparation of Morita–Baylis–Hillman Adducts 4: The appropriate aldehyde (220 mmol), acrylate (200 mmol), formamide (20 mmol, 0.8 mL) and DABCO (60 mmol, 6.73 g) were mixed at room temperature (additional 40 mL of DMSO were added in the cases of *p*-nitro- and *p*-chlorobenzaldehyde). After the conversion had reached at least 95% (from 8 h to 15 d, depending on the reactants, calculated by ^1H NMR analysis of a 5 μL sample of the reaction mixture diluted in $CDCl_3$), the reaction was directly submitted to chromatographic purification (*c*-hexane/ethyl acetate). The Morita–Baylis–Hillman adducts **4a**–**e** were obtained with high purity and in excellent yields (91, 88, 94, 86 and 90% for **4a**, **4b**, **4c**, **4d** and **4e**, respectively). Compounds **4a**, **4b**, **4c** and **4e** are known compounds.[13]

Ethyl 2-[Hydroxy(naphthalen-2-yl)methyl]acrylate (4d): The title compound was obtained in 86% yield as a pale-yellow oil. R_f = 0.20 (*c*-hexane/ethyl acetate = 8:2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.0 Hz, 3 H), 3.18 (br. d, J = 4.7 Hz, 1 H), 4.18 (q, J = 7.0 Hz, 2 H), 5.74 (br. d, J = 4.7 Hz, 1 H), 5.85 (s, 1 H), 6.38 (s, 1 H), 7.45–7.50 (m, 3 H), 7.81–7.87 (m, 4 H) ppm. ^{13}C NMR (100 MHz $CDCl_3$): δ = 14.0, 61.0, 73.2, 124.7, 125.6, 125.9, 126.0, 126.1, 127.7, 128.1, 128.2, 133.0, 133.2, 138.8, 142.3, 166.4 ppm. MS (ESI): m/z = 277 $[M + Na]^+$. $C_{16}H_{16}O_3$ (256.30): calcd. C 74.98, H 6.29; found C 74.88, H 6.17.

General Procedure for the Preparation of (*Z*)-2-Bromomethyl-2-alkenoates 6: Anhydrous LiBr (150 mmol, 13.3 g) was added to a solution of the appropriate Morita–Baylis–Hillman adduct **4** (100 mmol) in anhydrous DCM (40 mL) at room temperature. After cooling to 0 °C, 98% H_2SO_4 (4 mL) was rapidly added, the reaction vessel was tightly capped and then the reaction was allowed to warm to room temperature under vigorous stirring for 1.5 h. In the case of **4e** the entire reaction was performed at 0 °C. After dilution with diethyl ether (200 mL), the organic phase was washed with water (3 × 50 mL), dried (Na_2SO_4) and evaporated under reduced pressure at room temperature (***Caution:*** Derivative **6a** and, to a much greater extent **6e**, are volatile. In these cases the evaporation was carried out only with a rotary evaporator at room temp. In particular for **6e** it was necessary to absolutely avoid the use of the bath and to stop the evaporation before the flask had reached room temperature.) The products **6a**–**d** were obtained nearly pure and in almost quantitative yield. On the other hand, **6e** required purification on a short column of silica gel (petroleum ether/Et_2O, 95:5) and careful evaporation with the cautions mentioned above. Compound **6e** was stored at –18 °C. The *E* isomers, sometimes present in up to 3%, were not characterized.

Methyl (*Z*)-2-Bromomethyl-3-phenylpropenoate (6a): The title compound was obtained in quantitative yield as a pale-green oil. R_f = 0.26 (petroleum ether/Et_2O = 9:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 4.41 (s, 2 H), 7.40–7.50 (m, 3 H), 7.57–7.60 (m, 2 H), 7.84 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.9, 52.6, 128.8, 129.0, 129.8, 134.4, 143.1, 166.8 ppm. MS (ESI): m/z 277 $[M(^{79}Br) + Na]^+$, 279 $[M(^{81}Br) + Na]^+$. $C_{11}H_{11}BrO_2$ (255.11): calcd. C 51.79, H 4.35; found C 51.44, H 4.19.

Methyl (*Z*)-2-Bromomethyl-3-(4-nitrophenyl)propenoate (6b): The title compound was obtained in quantitative yield as pale-yellow crystals. R_f = 0.22 (petroleum ether/Et_2O = 7:3); m.p. 125–127 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 3 H), 4.31 (s, 2 H), 7.71–7.74 (m, 2 H), 7.83 (s, 1 H), 8.31–8.34 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 53.0, 124.2, 130.3, 132.1, 140.0, 140.7, 148.0, 166.0 ppm. MS (ESI): m/z 322 $[M(^{79}Br) + Na]^+$, 324

[M(^{81}Br) + Na]$^+$. $C_{11}H_{10}BrNO_4$ (300.11): calcd. C 44.02, H 3.36; found C 43.84, H 3.18.

Ethyl (*Z*)-2-Bromomethyl-3-(4-chlorophenyl)propenoate (6c): The title compound was obtained in quantitative yield as a white powder. Recrystallization from Et_2O furnished white crystals. R_f = 0.33 (petroleum ether/Et_2O = 9:1); m.p. 56–58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, J = 7.2 Hz, 3 H), 4.30 (q, J = 7.2 Hz, 2 H), 4.35 (s, 2 H), 7.42–7.45 (m, 2 H), 7.50–7.53 (m, 2 H), 7.75 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 26.5, 61.7, 129.3, 129.7, 131.1, 132.9, 135.8, 141.4, 166.0 ppm. MS (ESI): *m*/*z* 325 [M(^{79}Br,^{35}Cl) + Na]$^+$, 327 [M(^{81}Br,^{35}Cl) + Na]$^+$. $C_{12}H_{12}BrClO_2$ (303.58): calcd. C 47.48, H 3.98; found C 47.24, H 3.78.

Ethyl (*Z*)-2-Bromomethyl-3-(2-naphthyl)propenoate (6d): The title compound was obtained in quantitative yield as a pale-yellow viscous oil. R_f = 0.23 (petroleum ether/Et_2O = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (t, J = 7.0 Hz, 3 H), 4.37 (q, J = 7.0 Hz, 2 H), 4.49 (s, 2 H), 7.52–7.58 (m, 2 H), 7.64–7.66 (m, 1 H), 7.85–7.88 (m, 1 H), 7.90–7.93 (m, 2 H), 7.98 (s, 1 H), 8.12 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 27.2, 61.6, 126.5, 126.8, 127.5, 127.8, 128.7, 128.8, 129.1, 130.0, 131.9, 133.2, 133.5, 142.9, 166.3 ppm. MS (ESI): *m*/*z* 341 [M(^{79}Br) + Na]$^+$, 343 [M(^{81}Br) + Na]$^+$. $C_{16}H_{15}BrO_2$ (319.20): calcd. C 45.98, H 6.43; found C 60.04, H 4.58.

Methyl (*Z*)-2-Bromomethyl-5-methyl-2-hexenoate (6e): The title compound was obtained in 90% yield as a colourless oil. R_f = 0.28 (petroleum ether/Et_2O = 98:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, J = 6.6 Hz, 6 H), 1.77–1.90 (m, 1 H), 2.19 (dd, J = 6.6, 7.8 Hz, 2 H), 3.80 (s, 3 H), 4.23 (s, 2 H), 7.00 (t, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7, 24.5, 28.2, 38.0, 52.3, 129.8, 147.6, 166.2 ppm. MS (ESI): *m*/*z* 257 [M(^{79}Br) + Na]$^+$, 259 [M(^{81}Br) + Na]$^+$. $C_9H_{15}BrO_2$ (235.12): calcd. C 45.98, H 6.43; found C 45.76, H 6.29.

General Procedure for the Formation of Amino Esters 7a–e, *ent*-7a–e, 8a–e and *ent*-8a–e: The following procedure refers to the conditions optimized to obtain predominantly **7a**–**e** (Conditions i. in the text). See below for the modifications used to obtain predominantly *ent*-**7a**–**e** (Conditions ii. in the text), **8a**–**e** or *ent*-**8a**–**e**, for the reactions performed during the optimization of the experimental conditions and for the recycling of quinine or quinidine. Quinidine (3.6 g, 11 mmol) was added to a solution of compound **6a**–**e** (10 mmol) in dry DCM (20 mL) at room temp. After stirring for 3 h, the reaction was cooled in an ice bath and then (*S*)-1-(4-methoxyphenyl)ethylamine (**5**; 1.63 mL, 11 mmol) was added. The reaction mixture was stirred for 1 h (2 h in the case of **6d**) at 0 °C and then poured into a mixture of petroleum ether (150 mL) and NaOH 1 M (15 mL) under vigorous stirring. The precipitate was filtered and washed with petroleum ether (3 × 30 mL) and then the organic phase was separated, dried with anhydrous Na_2SO_4 and the solvents evaporated under vacuum [***Caution:*** the presence of other bases, i.e., residual quantities of quinidine and (*S*)-1-(4-methoxyphenyl)ethylamine, catalyses the rearrangement of products to the unwanted aminomethyl derivatives. Then, to slightly improve the yields, it was useful to avoid completely the use of the warming bath and to stop the evaporation before the flask reached room temperature]. Compounds **7a**–**e** were obtained pure after chromatographic purification (petroleum ether/Et_2O) and careful concentration, avoiding the use of any warming [***Caution:*** at room temp. the neat pure products undergo slow rearrangement to aminomethyl derivatives (up to 5% in a day) and must then be stored at –18 °C].

Compounds **8a**–**e** were obtained as the predominant isomers by following the same procedure, but by using quinine and (*S*)-1-(4-methoxyphenyl)ethylamine (**5**; entry b, Table 3).

Compounds *ent*-**7a**–**e** were obtained as the predominant isomers by performing the reaction with quinine and (*R*)-1-(4-methoxyphenyl)ethylamine (*ent*-**5**; Conditions ii. in the text), whereas compounds *ent*-**8a**–**e** were obtained as the predominant isomers by using quinidine and (*R*)-1-(4-methoxyphenyl)ethylamine (*ent*-**5**; entry a, Table 4).

The experimental conditions were optimized on a 1 mmol scale of **6a** following the general procedure but by using the conditions (solvent, tertiary base and time) reported in Tables 2–4. When cinchonine was used as the tertiary base, a mixture of DCM (1 mL) and MeOH (1 mL) was used as solvent. Then the solvent was eliminated under vacuum at room temperature and only DCM (2 mL) was added before the addition of (*S*)-1-(4-methoxyphenyl)ethylamine (**5**) at 0 °C.

Quinidine and quinine (for the reaction carried out on a 10 mmol scale) were recycled by carefully washing the precipitate with additional petroleum ether (30 mL) and cold water (20 mL), and then drying at 80 °C overnight. In general, 75–90% of the bases were recovered.

The reaction carried out on a 100 mmol scale of **6a** under Conditions i. was performed with the same proportion of reagents and solvents as indicated above in the general procedure.

Methyl 2-[(*R*)-{[(*S*)-1-(4-Methoxyphenyl)ethyl]amino}(phenyl)methyl]acrylate (7a) and Methyl 2-[(*S*)-{[(*R*)-1-(4-Methoxyphenyl)-ethyl]amino}(phenyl)methyl]acrylate (*ent*-7a): Compounds **7a** and *ent*-**7a** were obtained, respectively, in 89 (Conditions i.) and 84% yields (Conditions ii.) as pale-yellow viscous oils. In the case of the reaction performed on a 100 mmol scale of **6a** under Conditions i., **7a** was obtained in 85% yield. In the case of the reaction of **6a** with recovered quinidine and (*S*)-(–)-1-(4-methoxyphenyl)ethylamine (**5**), **7a** was obtained in 82% yield, whereas the reaction of **6a** with recovered quinine and (*R*)-(–)-1-(4-methoxyphenyl)ethylamine (*ent*-**5**) gave *ent*-**7a** in 80% yield. R_f = 0.36 (petroleum ether/Et_2O = 1:1). $[a]_D^{20}$ (**7a**) = –75 (*c* = 1.00, $CHCl_3$). $[a]_D^{20}$ (*ent*-**7a**) = +77 (*c* = 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (d, J = 6.6 Hz, 3 H), 1.88 (br. s, 1 H), 3.57 (q, J = 6.6 Hz, 1 H), 3.63 (s, 3 H), 3.81 (s, 3 H), 4.46 (s, 1 H), 5.77–5.78 (m, 1 H), 6.23 (s, 1 H), 6.84–6.88 (m, 2 H), 7.14–7.18 (m, 2 H), 7.23–7.27 (m, 3 H), 7.23–7.27 (m, 3 H), 7.29–7.34 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 51.8, 54.5, 55.3, 60.1, 113.8, 125.4, 127.3, 127.9, 128.0, 128.4, 137.3, 141.6, 143.2, 158.7, 167.0 ppm. MS (ESI): *m*/*z* 348 [M + Na]$^+$. $C_{20}H_{23}NO_3$ (325.41): calcd. C 73.82, H 7.12, N 4.30; found C 73.66, H 6.99, N 4.43.

Methyl 2-[(*S*)-{[(*S*)-1-(4-Methoxyphenyl)ethyl]amino}(phenyl)methyl]acrylate (8a) and Methyl 2-[(*R*)-{[(*R*)-1-(4-Methoxyphenyl)ethyl]-amino}(phenyl)methyl]acrylate (*ent*-8a): Compounds **8a** and *ent*-**8a** were obtained, respectively, in 51 [reaction with quinine and (*S*)-(–)-1-(4-methoxyphenyl)ethylamine (**5**)] and 67% yields [reaction with quinidine and (*R*)-(+)-1-(4-methoxyphenyl)ethylamine (*ent*-**5**)] as pale-yellow viscous oils. R_f = 0.47 (petroleum ether/Et_2O = 1:1). $[a]_D^{20}$ (**8a**) = +51 (*c* = 1.00, $CHCl_3$). $[a]_D^{20}$ (*ent*-**8a**) = –50 (*c* = 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (d, J = 6.6 Hz, 3 H), 1.95 (br. s, 1 H), 3.64 (s, 3 H), 3.72 (q, J = 6.6 Hz, 1 H), 3.80 (s, 3 H), 4.43 (s, 1 H), 5.88–5.89 (m, 1 H), 6.39–6.40 (m, 1 H), 6.84–6.87 (m, 2 H), 7.18–7.31 (m, 7 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 51.8, 54.7, 55.4, 60.6, 114.0, 126.2, 127.1, 127.2, 127.8, 128.4, 137.7, 141.1, 142.2, 158.7, 166.9 ppm. MS (ESI): *m*/*z* 348 [M + Na]$^+$. $C_{20}H_{23}NO_3$ (325.41): calcd. C 73.82, H 7.12, N 4.30; found C 73.68, H 7.02, N 4.46.

Methyl 2-[(*R*)-{[(*S*)-1-(4-Methoxyphenyl)ethyl]amino}(4-nitrophenyl)methyl]acrylate (7b) and Methyl 2-[(*S*)-{[(*R*)-1-(4-Meth-

oxyphenyl)ethyl]amino}(4-nitrophenyl)methyl]acrylate (*ent*-7b): Compounds **7b** and *ent*-**7b** were obtained, respectively, in 78 (Conditions i.) and 81% yields (Conditions ii.) as colourless waxes that solidified on standing to form colourless needles; m.p. 59–61 °C. R_f = 0.14 (petroleum ether/Et_2O = 7:3). $[\alpha]_D^{20}$ (**7b**) = –101 (*c* = 0.55, DCM). $[\alpha]_D^{20}$ (*ent*-**7b**) = +102 (*c* = 0.70, DCM). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 6.6 Hz, 3 H), 1.73 (br. s, 1 H), 3.51 (q, *J* = 6.6 Hz, 1 H), 3.63 (s, 3 H), 3.81 (s, 3 H), 4.55 (s, 1 H), 5.89 (m, 1 H), 6.32 (s, 1 H), 6.85–6.89 (m, 2 H), 7.10–7.13 (m, 2 H), 7.44–7.48 (m, 2 H), 8.16–8.19 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 52.0, 54.7, 55.4, 59.6, 114.1, 123.7, 126.4, 127.8, 128.8, 136.7, 142.0, 147.3, 149.6, 158.9, 166.4 ppm. MS (ESI): *m*/*z* 393 $[M + Na]^+$. $C_{20}H_{22}N_2O_5$ (370.40): calcd. C 64.85, H 5.99, N 7.56; found C 68.71, H 5.82, N 7.43.

Methyl 2-[(*S*)-{[(*S*)-1-(4-Methoxyphenyl)ethyl]amino}(4-nitrophenyl)methyl]acrylate (8b) and Methyl 2-[(*R*)-{[(*R*)-1-(4-Methoxyphenyl)ethyl]amino}(4-nitrophenyl)methyl]acrylate (*ent*-8b): Compounds **8b** and *ent*-**8b** were obtained, respectively, in 47 [reaction with quinine and (*S*)(–)-1-(4-methoxyphenyl)ethylamine (**5**)] and 65% yields [reaction with quinidine and (*R*)-(+)-1-(4-methoxyphenyl)ethylamine (*ent*-**5**)] as pale-yellow waxes. R_f = 0.34 (petroleum ether/Et_2O = 7:3). $[\alpha]_D^{20}$ (**8b**) = +39 (*c* = 2.00, DCM). $[\alpha]_D^{20}$ (*ent*-**8b**) = –40 (*c* = 1.83, DCM). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.6 Hz, 3 H), 2.07 (br. s, 1 H), 3.66 (s, 3 H), 3.75 (q, *J* = 6.6 Hz, 1 H), 3.79 (s, 3 H), 4.40 (s, 1 H), 5.84 (m, 1 H), 6.48 (s, 1 H), 6.83–6.87 (m, 2 H), 7.20–7.24 (m, 2 H), 7.51–7.54 (m, 2 H), 8.10–8.14 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0, 52.0, 54.9, 55.4, 60.8, 114.1, 123.5, 127.8, 128.0, 136.9, 139.6, 147.0, 150.0, 158.9, 166.3 ppm. MS (ESI): *m*/*z* 393 $[M + Na]^+$. $C_{20}H_{22}N_2O_5$ (370.40): calcd. C 64.85, H 5.99, N 7.56; found C 68.68, H 5.85, N 7.46.

Ethyl 2-[(*R*)-(4-Chlorophenyl){[(*S*)-1-(4-methoxyphenyl)ethyl]amino}methyl]acrylate (7c) and Ethyl 2-[(*S*)-(4-Chlorophenyl){[(*R*)-1-(4-methoxyphenyl)ethyl]amino}methyl]acrylate (*ent*-7c): Compounds **7c** and *ent*-**7c** were obtained, respectively, in 86 (Conditions i.) and 89% yields (Conditions ii.) as pale-yellow oils. R_f = 0.12 (petroleum ether/Et_2O = 7:3). $[\alpha]_D^{20}$ (**7c**) = –92 (*c* = 1.50, $CHCl_3$). $[\alpha]_D^{20}$ (*ent*-**7c**) = +90 (*c* = 1.28, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.1 Hz, 3 H), 1.30 (d, *J* = 6.6 Hz, 3 H), 1.60 (br. s, 1 H), 3.54 (q, *J* = 6.6 Hz, 1 H), 3.81 (s, 3 H), 4.04 (q, *J* = 7.1 Hz, 0.2 H), 4.07 (q, *J* = 7.1 Hz, 0.8 H), 4.09 (q, *J* = 7.1 Hz, 0.8 H), 4.12 (q, *J* = 7.1 Hz, 0.2 H), 4.43 (s, 1 H), 5.78–5.79 (m, 1 H), 6.25 (s, 1 H), 6.84–6.88 (m, 2 H), 7.12–7.16 (m, 2 H), 7.18–7.21 (m, 2 H), 7.26–7.30 (m, 2 H) ppm [$CO_2CH_2CH_3$ signal shows 2 major and 2 minor resonances due to the presence of rotamers]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 24.6, 54.5, 55.3, 59.4, 60.8, 113.9, 125.3, 127.8, 128.5, 129.3, 132.9, 137.0, 140.3, 143.0, 158.7, 166.3 ppm. MS (ESI): *m*/*z* 396 $[M(^{35}Cl)+Na]^+$. $C_{21}H_{24}ClNO_3$ (373.88): calcd. C 67.46, H 6.47, N 3.75; found C 67.31, H 6.35, N 3.56.

Ethyl 2-[(*S*)-(4-Chlorophenyl){[(*S*)-1-(4-methoxyphenyl)ethyl]amino}methyl]acrylate (8c) and Ethyl 2-[(*R*)-(4-Chlorophenyl){[(*R*)-1-(4-methoxyphenyl)ethyl]amino}methyl]acrylate (*ent*-8c): Compounds **8c** and *ent*-**8c** were obtained, respectively, in 62 [reaction with quinine and (*S*)-(–)-1-(4-methoxyphenyl)ethylamine (**5**)] and 65% yields [reaction with quinidine and (*R*)-(+)-1-(4-methoxyphenyl)ethylamine (*ent*-**5**)] as pale-yellow oils. R_f = 0.26 (petroleum ether/Et_2O = 7:3). $[\alpha]_D^{20}$ (**8c**) = +61 (*c* = = 1.50, $CHCl_3$). $[\alpha]_D^{20}$ = (*ent*-**8c**) = –62 (*c* = 1.40, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.0 Hz, 3 H), 1.35 (d, *J* = 6.6 Hz, 3 H), 1.95 (br. s, 1 H), 3.72 (q, *J* = 7.0 Hz, 1 H), 3.80 (s, 3 H), 4.06 (q, *J* = 7.0 Hz, 0.1 H), 4.09 (q, *J* = 7.0 Hz, 0.9 H), 4.10 (q, *J* = 7.0 Hz, 0.9 H), 4.12 (q, *J* = 7.0 Hz, 0.1 H), 4.36 (s, 1 H), 5.80–5.81 (m, 1 H), 6.39–6.40 (m, 1 H), 6.83–6.87 (m, 2 H), 7.20–7.27 (m, 6 H) ppm [$CO_2CH_2CH_3$ signal shows 2 major and 2 minor resonances due to the presence of rotamers]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 24.8, 54.7, 55.4, 60.3, 60.8, 114.0, 126.5, 127.8, 128.4, 128.6, 132.7, 137.4, 140.8, 141.0, 158.8, 166.3 ppm. MS (ESI): *m*/*z* 396 $[M(^{35}Cl)+Na]^+$. $C_{21}H_{24}ClNO_3$ (373.88): calcd. C 67.46, H 6.47, N 3.75; found C 67.36, H 6.32, N 3.59.

Ethyl 2-[(*R*)-{[(*S*)-1-(4-Methoxyphenyl)ethyl]amino}(naphthalen-2-yl)methyl]acrylate (7d) and Ethyl 2-[(*S*)-{[(*R*)-1-(4-Methoxyphenyl)ethyl]amino}(naphthalen-2-yl)methyl]acrylate (*ent*-7d): Compounds **7d** and *ent*-**7d** were obtained, respectively, in 89 (Conditions i.) and 84% yields (Conditions ii.) as colourless oils. R_f = 0.25 (petroleum ether/Et_2O = 1:1). $[\alpha]_D^{20}$ (**7d**) = –185 (*c* = 2.00, DCM). $[\alpha]_D^{20}$ (*ent*-**7d**) = +187 (*c* = 2.15, DCM). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.0 Hz, 3 H), 1.32 (d, *J* = 6.6 Hz, 3 H), 1.99 (br. s, 1 H), 3.63 (q, *J* = 6.6 Hz, 1 H), 3.83 (s, 3 H), 4.05 (q, *J* = 7.0 Hz, 0.1 H), 4.07 (q, *J* = 7.0 Hz, 0.9 H), 4.10 (q, *J* = 7.0 Hz, 0.9 H), 4.13 (q, *J* = 7.0 Hz, 0.1 H), 4.66 (s, 1 H), 5.85 (s, 1 H), 6.39 (s, 1 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 7.19 (d, *J* = 8.6 Hz, 2 H), 7.41–7.50 (m, 3 H), 7.71 (s, 1 H), 7.81–7.85 (m, 3 H) ppm [$CO_2CH_2CH_3$ signal shows 2 major and 2 minor resonances due to the presence of rotamers]. ^{13}C NMR (100 MHz $CDCl_3$): δ = 14.2, 24.8, 54.5, 55.4, 60.1, 60.7, 113.9, 125.3, 125.8, 126.0, 126.1, 126.9, 127.7, 127.9, 128.0, 128.1, 132.9, 133.4, 137.3, 139.1, 143.4, 158.7, 166.6 ppm. MS (ESI): *m*/*z* 412 $[M + Na]^+$. $C_{25}H_{27}NO_3$ (389.49): calcd. C 77.09, H 6.99, N 3.60; found C 76.86, H 6.92, N 3.47.

Ethyl 2-[(*S*)-{[(*S*)-1-(4-Methoxyphenyl)ethyl]amino}(naphthalen-2-yl)methyl]acrylate (8d) and Ethyl 2-[(*R*)-{[(*R*)-1-(4-Methoxyphenyl)ethyl]amino}(naphthalen-2-yl)methyl]acrylate (*ent*-8d): Compounds **8d** and *ent*-**8d** were obtained, respectively, in 53 [reaction with quinine and (*S*)-(–)-1-(4-methoxyphenyl)ethylamine (**5**)] and 60% yields [reaction with quinidine and (*R*)-(+)-1-(4-methoxyphenyl)ethylamine (*ent*-**5**)] as pale-yellow oils. R_f = 0.42 (petroleum ether/Et_2O = 1:1). $[\alpha]_D^{20}$ (**8d**) = +80 (*c* = 2.00, DCM). $[\alpha]_D^{20}$ (*ent*-**8d**) = –78 (*c* = 1.45, DCM). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.0 Hz, 3 H), 1.39 (d, *J* = 6.6 Hz, 3 H), 1.98 (br. s, 1 H), 3.79 (q, *J* = 6.6 Hz, 1 H), 3.80 (s, 3 H), 4.05 (q, *J* = 7.0 Hz, 0.1 H), 4.08 (q, *J* = 7.0 Hz, 0.9 H), 4.08 (q, *J* = 7.0 Hz, 0.9 H), 4.11 (q, *J* = 7.0 Hz, 0.1 H), 4.63 (s, 1 H), 5.93 (s, 1 H), 6.45 (d, *J* = 1.6 Hz, 1 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 7.25 (d, *J* = 8.6 Hz, 2 H), 7.41–7.47 (m, 3 H), 7.75–7.81 (m, 4 H) ppm [$CO_2CH_2CH_3$ signal shows 2 major and 2 minor resonances due to the presence of rotamers]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 24.6, 54.8, 55.4, 60.6, 60.7, 114.0, 125.7, 125.8, 125.9, 126.0, 126.1, 127.7, 127.9, 128.0, 128.1, 132.8, 133.5, 137.7, 139.8, 141.4, 158.7, 166.5 ppm. MS (ESI): *m*/*z* 412 $[M + Na]^+$. $C_{25}H_{27}NO_3$ (389.49): calcd. C 77.09, H 6.99, N 3.60; found C 76.94, H 6.89, N 3.49.

Methyl (*R*)-3-{[(*S*)-1-(4-Methoxyphenyl)ethyl]amino}-5-methyl-2-methylenehexanoate (7e) and Methyl (*S*)-3-{[(*R*)-1-(4-Methoxyphenyl)ethyl]amino}-5-methyl-2-methylenehexanoate (*ent*-7e): Compounds **7e** and *ent*-**7e** were obtained, respectively, in 72 (Conditions i.) and 60% yields (Conditions ii.) as colourless oils. R_f = 0.04 (petroleum ether/Et_2O = 6:4). $[\alpha]_D^{20}$ (**7e**) = –46 (*c* = 0.67, DCM). $[\alpha]_D^{20}$ (*ent*-**7e**) = +46 (*c* = 0.85, DCM). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 1.26 (d, *J* = 6.2 Hz, 3 H), 1.45 (t, *J* = 7.0 Hz, 2 H), 1.57–1.70 (br. s + m, 2 H), 3.56 (t, *J* = 7.0 Hz, 1 H), 3.68 (q, *J* = 6.2 Hz, 1 H), 3.72 (s, 3 H), 3.79 (s, 3 H), 5.58–5.59 (m, 1 H), 6.18–6.19 (s, 1 H), 6.81–6.85 (m, 2 H), 7.20–7.23 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6, 22.7, 22.9, 25.2, 44.6, 51.7, 54.2, 55.4, 56.3, 113.8, 125.6, 127.9, 138.6, 142.4, 158.6, 167.4 ppm. MS (ESI): *m*/*z* 328 [M +

Na]$^+$. $C_{18}H_{27}NO_3$ (305.42): calcd. C 70.79, H 8.91, N 4.59; found C 70.64, H 8.81, N 4.43.

Methyl (*S*)-3-{[(*S*)-1-(4-Methoxyphenyl)ethyl]amino}-5-methyl-2-methylenehexanoate (8e) and Methyl (*R*)-3-{[(*R*)-1-(4-Methoxyphenyl)eth-yl]amino}-5-methyl-2-methylenehexanoate (*ent*-8e): Compounds **8e** and *ent*-**8e** were obtained, respectively, in 45 [reaction with quinine and (*S*)-(–)-1-(4-methoxyphenyl)ethylamine (**5**)] and 50% yields [reaction with quinidine and (*R*)-(+)-1-(4-methoxyphenyl)ethylamine (*ent*-**5**)] as colourless oils. R_f = 0.15 (petroleum ether/Et_2O = 6:4). $[\alpha]_D^{20}$ (**8e**) = –28 (*c* = 2.00, DCM). $[\alpha]_D^{20}$ (*ent*-**8e**) = +29 (*c* = 1.65, DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.71 (d, *J* = 6.2 Hz, 3 H), 0.78 (d, *J* = 6.6 Hz, 3 H), 1.24 (d, *J* = 6.6 Hz, 3 H), 1.30–1.37 (m, 1 H), 1.41–1.48 (m, 1 H), 1.55–1.70 (br. s + m, 2 H), 3.09 (dd, *J* = 6.4, 8.0 Hz, 1 H), 3.61 (q, *J* = 6.6 Hz, 1 H), 3.75 (s, 3 H), 3.80 (s, 3 H), 5.41–5.42 (m, 1 H), 6.16–6.17 (m, 1 H), 6.83–6.86 (m, 2 H), 7.18–7.22 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 23.0, 25.0, 25.6, 45.0, 51.7, 54.3, 55.3, 56.8, 113.8, 125.9, 128.0, 137.7, 141.9, 158.6, 167.3 ppm. MS (ESI): *m*/*z* = 328 [M + Na]$^+$. $C_{18}H_{27}NO_3$ (305.42): calcd. C 70.79, H 8.91, N 4.59; found C 70.59, H 8.78, N 4.46.

Methyl (*S*,*E*)-2-({[1-(4-Methoxyphenyl)ethyl]amino}methyl)-3-phenylacrylate (9): The title compound was obtained in 79% yield as a pale-yellow viscous oil (reaction with Et_3N in DMSO, as in Table 2, but with a reaction time of 3 d at room temperature). R_f = 0.11 (*c*-hexane/ethyl acetate = 2:8). $[\alpha]_D^{20}$ = –107 (*c* = 1.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 7.0 Hz, 3 H), 1.74 (br. s, 1 H), 3.41 (d, *J* = 11.7 Hz, 1 H), 3.46 (d, *J* = 11.7 Hz, 1 H), 3.74 (q, *J* = 7.0 Hz, 1 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 6.82–6.86 (m, 2 H), 7.21–7.31 (m, 5 H), 7.35–7.37 (m, 2 H), 7.76 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 44.4, 52.2, 55.4, 58.0, 113.8, 128.1, 128.5, 128.9, 129.7, 130.7, 135.1, 137.4, 141.9, 158.7, 168.8 ppm. MS (ESI): *m*/*z* 348 [M + Na]$^+$. $C_{20}H_{23}NO_3$ (325.41): calcd. C 73.82, H 7.12, N 4.30; found C 73.69, H 7.03, N 4.16.

General Procedure for the Synthesis of Enantiomerically Pure Protected 2-Methylene-3-amino Esters 10 and *ent*-10: Compounds **7a**–**e** or *ent*-**7a**–**e** (5 mmol), were dissolved in trifluoroacetic acid (10 mL) and the reactions were heated at reflux for 8 h (72 h in the case of **7e**) using a condenser equipped with an anhydrous $CaCl_2$ trap. After elimination of the trifluoroacetic acid under vacuum (bath temperature of 60 °C), the residue was dissolved in DCM (3 mL) and THF (5 mL), and the solvent was carefully evaporated. The procedure was repeated five times and then di-*tert*-butyl dicarbonate (7.5 mmol, 1.64 g) and 1 M NaOH (15 mL) were sequentially added to the residue dissolved in DCM (10 mL) at room temperature. The pH of the aqueous phase was verified to be ≥13; if it was not, additional aliquots of 1 mL of 1 M NaOH were added until the pH was above this value. The reaction mixture was stirred for 2 h, diluted with DCM (20 mL) and water (10 mL) and, after separation, the aqueous phase was extracted again with DCM (2 × 10 mL). The unified organic phases were dried with anhydrous Na_2SO_4, the solvent was eliminated under vacuum and the residue was submitted to silica gel chromatographic purification (from *c*-hexane/DCM to DCM/methanol) to obtain the pure products **10a**–**e** or *ent*-**10a**–**e**. The *ee* values of the enantiomers **10a**–**e** were ≥96 or ≥98%, whereas those of *ent*-**10a**–**e** were ≥98 or ≥99%, depending on the enantiomeric purity of the chiral inducer used (see Materials section).

Methyl (*R*)-2-{[(*tert*-Butoxycarbonyl)amino](phenyl)methyl}acrylate (10a) and Methyl (*S*)-2-{[(*tert*-Butoxycarbonyl)amino](phenyl)-methyl}acrylate (*ent*-10a): The title compounds were obtained in 85% yields from **7a** and *ent*-**7a**, respectively, as colourless waxes that solidified on standing to form white crystals. Recrystallization from *c*-hexane/ethyl acetate furnished colourless crystals; m.p. 76–78 °C. R_f = 0.23 (DCM). The *ee* values of the products were determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*PrOH, 99:1, flow rate 0.3 mL/min, λ = 210 nm, $t_{ent\text{-}\mathbf{10a}}$ = 27.8 min, t_{10a} = 29.0 min, *ee* ≥ 99% when (*S*)-(–)-1-(4-methoxyphenyl)ethylamine (**5**) with ≥98.5% *ee* and (*R*)-(–)-1-(4-methoxyphenyl)ethylamine (*ent*-**5**) with ≥99% *ee* were used, see the Materials section]. $[\alpha]_D^{20}$ (**10a**) = –23 (*c* = 1.05, $CHCl_3$). $[\alpha]_D^{20}$ (*ent*-**10a**) = +22 (*c* = 0.75, $CHCl_3$). The absolute configurations of compounds **10a** and *ent*-**10a** were determined by comparison with the literature values: $[\alpha]_D^{20}$ (**10a**) = –15.1 (*c* = 0.15, $CHCl_3$), 77% *ee*.[6d] $[\alpha]_D^{20}$ (*ent*-**10a**) = +21 (*c* = 0.68, $CHCl_3$), 91% *ee*.[6c] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 3.67 (s, 3 H), 5.48 (br. s, 1 H), 5.68 (br. d, *J* = 8.2 Hz, 1 H), 5.92 (s, 1 H), 6.37 (s, 1 H), 7.23–7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5, 52.0, 56.3, 80.0, 126.7, 127.6, 128.7, 140.0, 155.1, 166.3 ppm. MS (ESI): *m*/*z* 314 [M + Na]$^+$. $C_{16}H_{21}NO_4$ (291.35): calcd. C 65.96, H 7.27, N 4.81; found C 65.79, H 7.14, N 4.67.

Methyl (*R*)-2-{[(*tert*-Butoxycarbonyl)amino](4-nitrophenyl)methyl}acrylate (10b) and Methyl (*S*)-2-{[(*tert*-Butoxycarbonyl)amino](4-nitrophenyl)methyl}acrylate (*ent*-10b): The title compounds were obtained in 72% yields from **7b** and *ent*-**7b**, respectively, as pale-yellow waxes. R_f = 0.17 (DCM). The *ee* values of the products were determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*PrOH, 95:5, flow rate 0.3 mL/min, λ = 210 nm, $t_{ent\text{-}\mathbf{10b}}$ = 34.6 min, t_{10b} = 36.5 min, *ee* 99% when (*S*)-(–)-1-(4-methoxyphenyl)ethylamine (**5**) with ≥98.5% *ee* and (*R*)-(–)-1-(4-methoxyphenyl)ethylamine (*ent*-**5**) with ≥99% *ee* were used, see Materials section]. $[\alpha]_D^{20}$ (**10b**) = +26 (*c* = 1.75, DCM). $[\alpha]_D^{20}$ (*ent*-**10b**) = –27 (*c* = 1.88, DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 3.70 (s, 3 H), 5.68–5.76 (m, 2 H), 6.00 (s, 1 H), 6.43 (s, 1 H), 7.46–7.49 (m, 2 H), 8.16–8.20 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4, 52.2, 56.2, 80.4, 123.8, 127.3, 128.6, 138.9, 147.3, 147.7, 155.0, 165.8 ppm. MS (ESI): *m*/*z* = 359 [M + Na]$^+$. $C_{16}H_{20}N_2O_6$ (336.34): calcd. C 57.14, H 5.99, N 8.33; found C 57.02, H 5.78, N 8.12.

Ethyl (*R*)-2-{[(*tert*-Butoxycarbonyl)amino](4-chlorophenyl)methyl}-acrylate (10c) and Ethyl (*S*)-2-{[(*tert*-Butoxycarbonyl)amino](4-chlorophenyl)methyl}acrylate (*ent*-10c): The title compounds were obtained in 80% yields from **7c** and *ent*-**7c**, respectively, as white waxes. Recrystallization from *c*-hexane/ethyl acetate furnished white crystals; m.p. 75–79 °C. R_f = 0.34 (DCM). The *ee* values of the products were determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*PrOH, 99:1, flow rate 0.3 mL/min, λ = 220 nm, $t_{ent\text{-}\mathbf{10c}}$ = 24.9 min, t_{10c} = 26.0 min, *ee* ≥ 99% when (*S*)-(–)-1-(4-methoxyphenyl)ethylamine (**5**) with ≥98.5% *ee* and (*R*)-(–)-1-(4-methoxyphenyl)ethylamine (*ent*-**5**) with ≥99% *ee* were used, see Materials section]. $[\alpha]_D^{20}$ (**10c**) = –8 (*c* = 2.00, $CHCl_3$). $[\alpha]_D^{20}$ (*ent*-**10c**) = +7 (*c* = 1.40, $CHCl_3$). The absolute configuration of compound **10c** was determined by comparison with the literature value: $[\alpha]_D^{20}$ (**10c**) = –5.3 (*c* = 0.51, $CHCl_3$), 90% *ee*.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.0 Hz, 3 H), 1.45 (s, 9 H), 4.09 (q, *J* = 7.0 Hz, 0.1 H), 4.12 (q, *J* = 7.0 Hz, 0.9 H), 4.13 (q, *J* = 7.0 Hz, 0.9 H), 4.15 (q, *J* = 7.0 Hz, 0.1 H), 5.49 (br. s, 1 H), 5.64 (d, *J* = 8.2 Hz, 1 H), 5.89 (s, 1 H), 6.37 (s, 1 H), 7.20–7.24 (m, 2 H), 7.27–7.30 (m, 2 H) ppm [$CO_2CH_2CH_3$ signal shows 2 major and 2 minor resonances due to the presence of rotamers]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 28.5, 55.8, 61.1, 80.1, 126.9, 128.0, 128.8, 133.3, 138.8, 140.0, 155.0, 165.6 ppm. MS (ESI): *m*/*z* = 362 [M(^{35}Cl) + Na]$^+$. $C_{17}H_{22}ClNO_4$ (339.82): calcd. C 60.09, H 6.53, N 4.12; found C 59.93, H 6.38, N 4.01.

Ethyl (*R*)-2-{[(*tert*-Butoxycarbonyl)amino](naphthalen-2-yl)methyl}-acrylate (10d) and Ethyl (*S*)-2-{[(*tert*-Butoxycarbonyl)amino]-

(naphthalen-2-yl)methyl}acrylate (*ent*-10d): The title compounds were obtained in 93% yields from **7d** and *ent*-**7d**, respectively, as pale-yellow waxes. Recrystallization from *c*-hexane furnished pale-yellow crystals; m.p. 98–101 °C. R_f = 0.36 (DCM). The *ee* values of the products were determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*PrOH, 99:1, flow rate 1.0 mL/min, λ = 210 nm, $t_{ent\text{-}10d}$ = 12.9 min, t_{10d} = 14.5 min, *ee* 99% when (*S*)-(–)-1-(4-methoxyphenyl)ethylamine (**5**) with ≥98.5% *ee* and (*R*)-(–)-1-(4-methoxyphenyl)ethylamine (*ent*-**5**) with ≥99% *ee* were used, see Materials section]. $[\alpha]_D^{20}$ (**10d**) = –40 (*c* = 2.00, DCM). $[\alpha]_D^{20}$ (*ent*-**10d**) = +41 (*c* = 1.53, DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.0 Hz, 3 H), 1.47 (s, 9 H), 4.07 (q, *J* = 7.0 Hz, 0.1 H), 4.09 (q, *J* = 7.0 Hz, 0.9 H), 4.10 (q, *J* = 7.0 Hz, 0.9 H), 4.13 (q, *J* = 7.0 Hz, 0.1 H), 5.55 (br. s, 1 H), 5.86 (d, *J* = 8.2 Hz, 1 H), 5.96 (s, 1 H), 6.43 (s, 1 H), 7.41–7.49 (m, 3 H), 7.73 (s, 1 H), 7.79–7.81 (m, 3 H) ppm [$CO_2CH_2CH_3$ signal shows 2 major and 2 minor resonances due to the presence of rotamers]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 28.5, 56.3, 61.0, 80.0, 125.1, 125.4, 126.1, 126.3, 126.4, 127.7, 128.1, 128.4, 132.8, 133.4, 137.6, 140.4, 155.1, 165.8 ppm. MS (ESI): *m*/*z* = 378 $[M + Na]^+$. $C_{21}H_{25}NO_4$ (355.43): calcd. C 70.96, H 7.09, N 3.94; found C 70.77, H 6.92, N 4.01.

Methyl (*R*)-3-[(*tert*-Butoxycarbonyl)amino]-5-methyl-2-methylenehexanoate (10e) and Methyl (*S*)-3-[(*tert*-Butoxycarbonyl)amino]-5-methyl-2-methylenehexanoate (*ent*-10e): The title compounds were obtained in 63% yields from **7e** and *ent*-**7e**, respectively, as colourless waxes. R_f = 0.30 (DCM). The *ee* values of the products were determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*PrOH, 99.5:0.5, flow rate 1.0 mL/min, λ = 210 nm, t_{10e} = 24.2 min, $t_{ent\text{-}10e}$ = 30.4 min, *ee* 99% when (*S*)-(–)-1-(4-methoxyphenyl)ethylamine (**5**) with ≥98.5% *ee* and (*R*)-(–)-1-(4-methoxyphenyl)ethylamine (*ent*-**5**) with ≥99% *ee* were used, see Materials section]. $[\alpha]_D^{20}$ (**10e**) = +11 (*c* = 1.22, $CHCl_3$). $[\alpha]_D^{20}$ (*ent*-**10e**) = –11 (*c* = 1.39, $CHCl_3$). The absolute configuration of compound *ent*-**10e** was determined by comparison with the literature value: $[\alpha]_D^{20}$ (*ent*-**10e**) = –10.6 (*c* = 1.00, $CHCl_3$).[1] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.6 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 1.42 (s, 9 H), 1.46–1.50 (m, 2 H), 1.53–1.63 (m, 1 H), 3.76 (s, 3 H), 4.39 (br. s, 0.2 H), 4.47 (dd, *J* = 7.8, 16.0 Hz, 0.8 H), 4.68 (br. s, 0.2 H), 5.12 (br. d, *J* = 8.6 Hz, 0.8 H), 5.67 (br. s, 0.2 H), 5.73 (s, 0.8 H), 6.16 (m, 1 H) ppm [some signals show multiple resonances due to the presence of rotamers]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 22.7, 25.2, 28.5, 44.0, 51.9, 79.4, 126.1, 140.9, 155.2, 166.6 ppm. MS (ESI): *m*/*z* = 294 $[M + Na]^+$. $C_{14}H_{25}NO_4$ (271.36): calcd. C 61.97, H 9.29, N 5.16; found C 61.76, H 8.98, N 5.02.

Supporting Information (see footnote on the first page of this article): Determination of the isomer ratio of quaternary ammonium salt intermediates, preliminary assignment of the configuration at C-3 in diastereomers **8a** and **9a** and NMR spectra of all new compounds.

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