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Chiral heterocyclic β-enamino esters: convenient synthesis and diastereoselective reduction

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Abstract—The preparation of chiral pyrrolidine and piperidine β-enamino esters starting from ω-halogeno β-keto esters, their diastereoselective reduction and the subsequent cleavage of the chiral auxiliary are described.

1. Introduction

During the course of our research toward the preparation of chiral polyfunctional heterocycles as precursors of natural products, we are interested in developing new methods able to spare sacrificial chiral auxiliaries by their introduction in a late stage of the synthesis. In a recent publication,[1] we described a convenient preparation of chiral pyrrolidine and piperidine β-enamino esters whose reduction products often constitute valuable intermediates in the synthesis of alkaloids.[2] This one-step procedure which involves the condensation of methyl ω-halogeno alcynoates and (*S*)-1-phenylethylamine or (*S*)-phenylglycinol (Scheme 1, route a), provides an interesting alternative to the Eschenmoser reaction,[3] (Scheme 1, route b) in which phosphorus-containing reagents may be troublesome.[4] We wish now to report our study concerning the condensation of the same chiral amines with ω-halogeno β-keto esters in place of the previously used but expensive alcynoates (Scheme 1, route c) to lead to various cyclic β-enamino esters. A study aimed at reducing the enamine moiety will be presented in a second part.

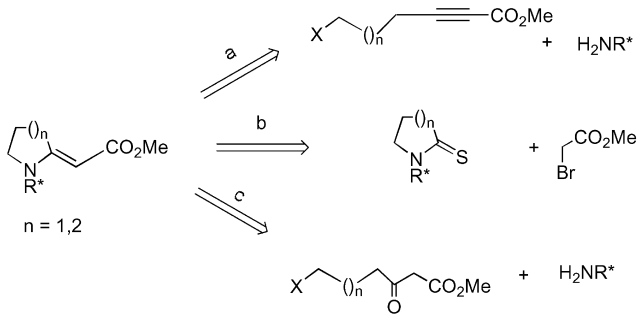
2. Results and discussion

2.1. Synthesis of chiral β-enamino esters

We first planed to synthesize pyrrolidine enamino esters **1** through an extension of a previously reported procedure[5] in which the authors reacted ethyl 6-chloro-3-oxohexanoate with various amines in the presence of catalytic iodine as a catalyst, sodium sulfate as a drying agent and disodium hydrogen phosphate as an acid scavenger (Scheme 2). Thus methyl 6-chloro-3-oxohexanoate[6] was reacted under these conditions with (*S*)-1-phenylethylamine or (*S*)-phenylglycinol yielding the expected compounds **1a** and **1b**, respectively, along with about 10% of the tetrahydrofuranyl derivative **2** resulting from the O-cycloalkylation of the starting chloro ester.[7] A simple acid-base workup followed by flash chromatography on silica gel gave **1a** and **1b** in 60 and 57% yield, respectively.

We then extended these results to the synthesis of the piperidine enamino esters **3** starting from methyl 7-chloro-3-oxoheptanoate.[6] However, condensation of the latter with (*S*)-1-phenylethylamine, in the conditions described above, exclusively afforded the undesired cyclohexene **5**[8] as the only identifiable product (Scheme 3, *conditions* (a)).

Analysis of the potential reactivity of 7-chloro-3-oxoheptanoate under the reaction conditions, indicates that this



Scheme 1.

Keywords: pyrrolidine; piperidine; enamino ester; β-keto ester; reduction; debenzylation.
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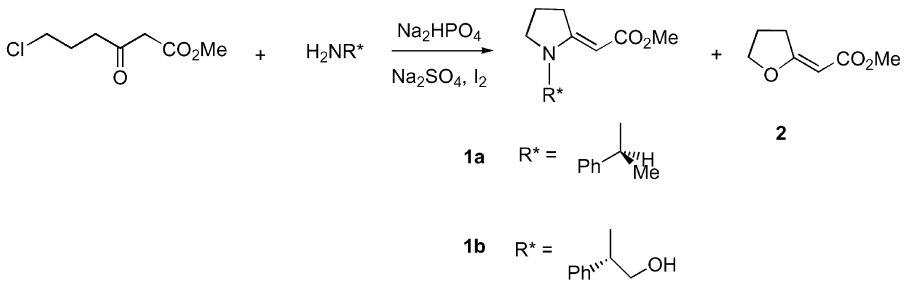
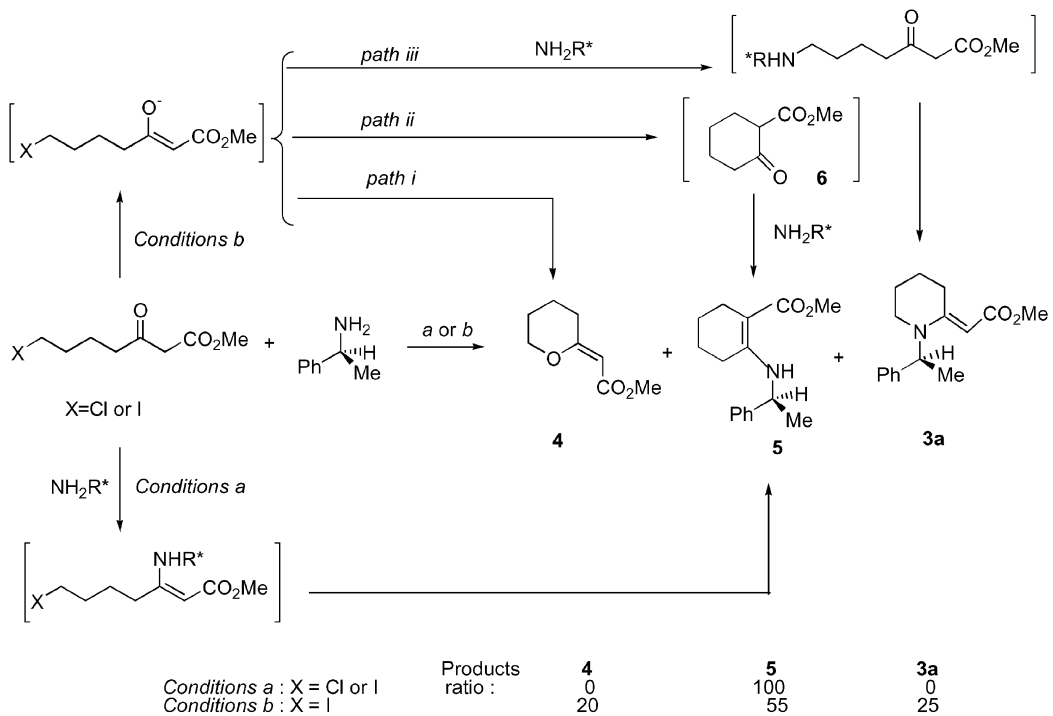


Scheme 2.

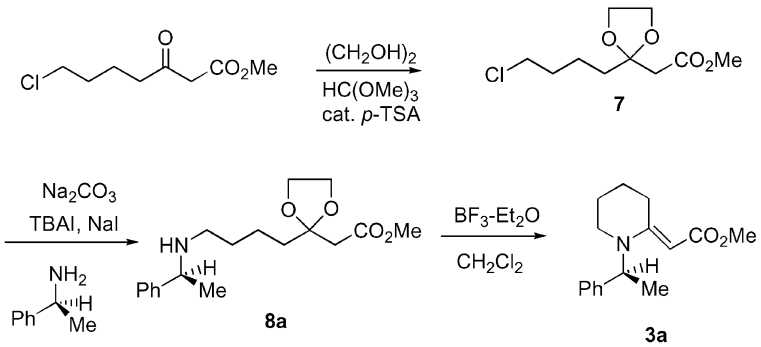
halogeno β-keto ester may evolve according to two competitive pathways, i.e. either into a ω-amino β-keto ester stemming from the initial substitution of the halogen by the chiral amine or into an enamine resulting from the reaction of the amine on the keto moiety. Our result clearly demonstrates that the latter intermediate is favored leading to compound **5** by a C-cycloalkylation process. It is noteworthy to mention that, in our previous alcynoate strategy,[1] we encountered similar problems that we finally overcame by replacing the chlorine by an iodine atom. This result prompted us to perform the reaction starting from methyl 7-iodo-3-oxoheptanoate readily obtained by treatment of the chloro analogue with NaI in refluxing acetone. However, **5** remained the only detected reaction product. The reaction was then attempted under conditions similar to those optimized with the alcynoates.[1] Thus, the iodo derivative was treated with an equimolar amount of (*S*)-1-phenylethylamine, in the presence of sodium carbonate (5 equiv.) and a catalytic amount of tetrabutylammonium iodide, in refluxing acetonitrile for 24 h. These reaction conditions led to the obtention of a mixture of the expected compound **3a** along with cyclohexene **5** and the tetrahydropyranyl derivative **4**[9] in a disappointing 25:55:20 ratio (Scheme 3, *conditions* (a)). Under these reaction conditions, the formation of the enolate of the β-keto ester is the first reaction to occur.[10] This intermediate may then evolve along three competitive pathways: either an O-cycloalkylation (as previously observed for the formation of **2**) to afford compound **4** (path i), or a C-cycloalkylation giving rise to cyclohexene **5** via the cyclic β-keto ester **6**[11] (path ii) or halogen displacement by the amine allowing the formation of the expected amino ester **3a** (path iii).

In view of this analysis, we reasoned that initial protection of the keto function of methyl 7-chloro-3-oxoheptanoate would prevent the generation of the enolate that was suspected to be the key intermediate of the observed side-products. Methyl 7-chloro-3-oxoheptanoate was thus readily converted into the corresponding dioxolane **7** in 82% yield. Subsequent substitution of the halogen moiety by (*S*)-1-phenylethylamine was achieved in refluxing acetonitrile in the presence of sodium iodide to promote the *in situ* halogen exchange, to afford amino dioxolane **8a** in 97% crude yield (Scheme 4).

At this point, we realized that the deprotection step of the dioxolane moiety could be followed by the *in situ* formation of the expected piperidine enamino ester **3a**. With this goal



Scheme 3. *Conditions* (a) Na_2SO_4, Na_2HPO_4, $[I_2]$; (b) Na_2CO_3, [TBAI], CH_3CN.



Scheme 4.

in mind, we screened various acidic conditions. The use of either Dowex 50 resin in acetone or *p*-TSA, in acetone or methanol, left the substrate unchanged. Treatment with an aqueous 1N HCl solution provided the expected compound **3a** along with the undesired linear decarboxylation product **9** (Figure 1). The relative ratio of these two products depended on the reaction time, the temperature and the amount of acid. A brief study was carried out to optimize the amount of **3a**. The best result was obtained upon using 5 equiv. of HCl solution, for 11 h, at room temperature. Under these conditions, **3a** was isolated in 46% yield after chromatography on silica gel. Only a trace of **9** was detected in the reaction mixture. Finally, we discovered that borontrifluoride etherate[12] provided milder conditions while preventing the decarboxylation process: the expected compound **3a** was thus cleanly obtained in 74% yield (Scheme 4).

This optimized strategy was then applied to (*S*)-phenylglycinol (Scheme 5). In this case, the substitution step from dioxolane **7** led to compound **8b** in 95% crude yield, whereas the deprotection–cyclisation step, under the borontrifluoride etherate conditions, directly delivered the bicyclic derivative **10**, in 67% yield, as an inseparable 90:10 mixture of diastereomers, rather than the expected enaminoester **3b**, as previously observed.[1] Noteworthy was the formation of the decarboxylation compound **11** (Figure 1) as a mixture of diastereomers when the reaction was carried out under uncontrolled acidic conditions or when compound **10** was treated in acidic medium. A study of the spectroscopic data of the major isomer of **11** allowed us to assign a *cis* relationship between the phenyl group and the angular methyl substituent.[13] By extension, we can then ascribe the same relative configuration for the major isomer of compound **10** (Scheme 5).

It is to be noted that in order to avoid the formation of the tetrahydrofuranyl derivative **2**, this multi-step procedure involving a protecting step of the keto function was equally applied to the formation of pyrrolidine compounds **1a** and **1b**. However, the overall yields from methyl-6-chloro-3-oxohexanoate (57 and 47%, respectively) were not better than those obtained by the direct route.

2.2. Diastereoselective reductions

The pyrrolidines and piperidines thus obtained might be intermediates in the chiral synthesis of natural products following a diastereoselective reduction of the enamine/hemiaminal moiety and the subsequent cleavage of the chiral auxiliary. As far as the 1(*S*)-phenylethyl *N*-substituted β-enamino esters **1a** and **3a** are concerned, this strategy has already been studied by us and others.[14] However, this was not the case for the phenylglycinol derivatives **1b** and **10** and we therefore decided to extend the scope of this strategy from these substrates. The reduction of the C–C double bond of the pyrrolidine substrate **1b** was first carried out either by catalytic hydrogenation or using an hydride in order to compare the resulting diastereoselectivity. Catalytic hydrogenation was performed under an atmospheric pressure of hydrogen using PtO_2 as the catalyst to yield quantitatively the expected amino ester **12** with a 90% diastereomeric excess (Scheme 6). Triacetoxyborohydride mediated reduction[15] proceeded cleanly but with a lower selectivity (d.e.=70%). These results were similar to those obtained under similar conditions from **1a**. Noteworthy was the degradation of **12** upon silica gel chromatography to lead, among others, to a lactone derivative as a consequence of an intramolecular transesterification. The major diastereomer **12** was alternatively easily isolated by simple crystallization in cyclohexane,[16] in 53% yield. At this point, X-ray analysis[17] was performed and indicated a 2*S* assignment to the absolute configuration of the newly

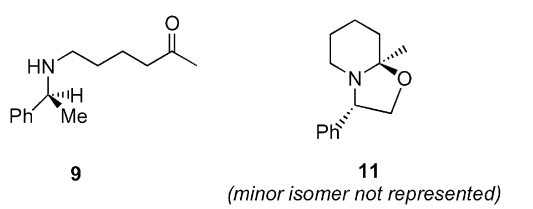
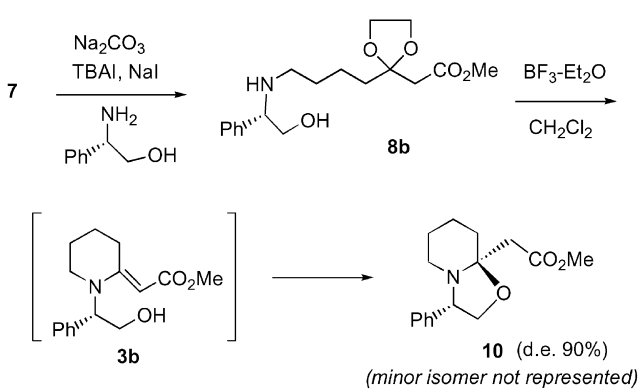
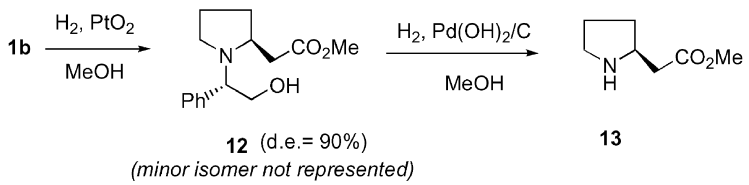


Figure 1.



Scheme 5.



Scheme 6.

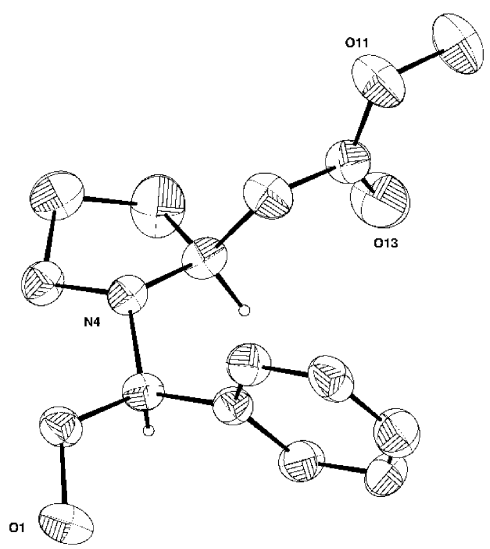


Figure 2. Crystal structure of **12**.

created stereocenter (Figure 2). Finally, debenzylation of **12** was readily achieved under an atmospheric pressure of hydrogen on $Pd(OH)_2/C$ affording quantitatively amino ester **13**.[18]

Concerning the diastereomeric mixture of bicyclic piperidine **10**, it should be stressed that catalytic hydrogenation over PtO_2 did not take place under neutral conditions. However, when performed in the presence of a catalytic amount of *p*-TSA, the expected compound **14** was obtained with a diastereomeric excess of 70%. This result suggested that the reaction proceeded through the reduction of an iminium intermediate. Improved results were observed upon triacetoxyborohydride reduction (Scheme 7). In this case, compound **14** was obtained as a mixture of diastereomers (d.e.=90%), in 93% yield, after column chromatography. The major isomer was isolated, in 63% yield, as an oil, following a second chromatography on silica gel. In contrast with the amino ester resulting from the reduction of **3a**,[14c] the debenzylation step proceeded smoothly under catalytic hydrogenation, on $Pd(OH)_2/C$, to give quantitatively rise to methyl piperidine-2-yl acetate **15**.[19] However, to our knowledge, literature does not mention any specific rotation for amine **15**, but for its *N*-*tert*-butoxycarbonyl derivative **16**.[20] Therefore, we transformed crude **15** into compound **16** in 90% overall chromatographed yield. Comparison of the spectroscopic data of the resulting compound[20] with the one described in the literature allowed us to secure the absolute configuration of **15** (and so of **14**) as 2(*S*). The stereochemistry of the major isomer of **14** results indeed from a favored approach of the hydrogen on the *Re* face of the iminium intermediate, in which 1,3-allylic strain is minimized (Scheme 7).

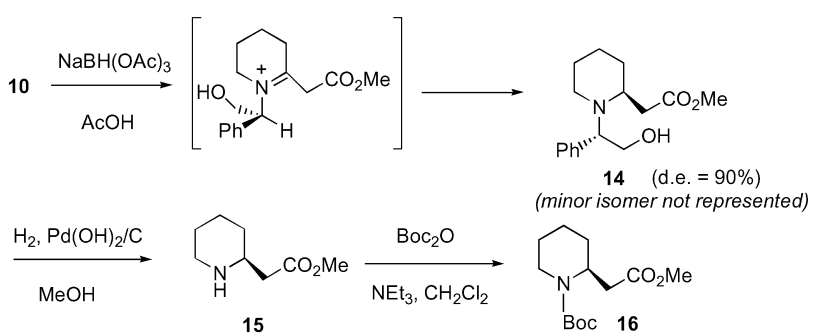
3. Conclusion

In conclusion, we have developed efficient alternative procedures for preparing enantiopure heterocyclic enamino esters from ω-halogeno β-keto esters and chiral amines. The compounds stemming from (*S*)-phenylglycinol have been reduced yielding with a high diastereoselectivity the corresponding amino esters, from which the chiral auxiliary moieties were subsequently smoothly removed. This strategy constitutes a valuable tool for the alkaloid synthesis and compares favorably with previously reported procedures in terms of cost, work up and ease of purification.

4. Experimental

4.1. General

Melting points were determined using a Buchi 535 apparatus and are uncorrected. IR spectra were recorded with a Philips PU 9706 spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ as solvent on a Bruker ARX 250 spectrometer with TMS or $CHCl_3$ as internal standard. The values of chemical shifts (δ) are given in ppm and



Scheme 7.

coupling constants (J) in Hertz. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Elemental analyses were performed by the Service Régional de Microanalyse de L'Université Pierre et Marie Curie. HRMS were obtained on a JEOL MS 700 mass spectrometer. Column chromatography was performed on Merk Kieselgel silica gel (230–400 mesh). All reactions were carried out in an argon atmosphere. Anhydrous CH_2Cl_2 was distilled from CaH_2. Anhydrous THF was distilled from sodium/benzophenone under nitrogen.

4.1.1. Methyl-6-chloro-3-oxohexanoate. To an ice-cooled stirred suspension of NaH (60% in oil, 2.2 g, 55 mmol) in anhydrous THF (100 mL) under argon was added dropwise methylacetoacetate (6.42 g, 55 mmol). The reaction mixture was stirred at 0°C for 30 min, afterwards *n*-BuLi (23.2 mL, 2.5 M solution in hexane, 58 mmol) was slowly added. After stirring for 30 min, the reaction mixture was cooled to −30°C, and 1-bromo-2-chloroethane (4.5 mL, 55 mmol) was added and stirring was continued at this temperature for 15 h. The mixture was then quenched by addition of saturated aqueous NH_4Cl solution (50 mL) and allowed to warm to room temperature. The reaction mixture was concentrated in vacuo and extracted with CH_2Cl_2 (150 mL). The organic layer was washed successively with saturated aqueous NH_4Cl solution (50 mL), water (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. Column chromatography eluting with ethyl acetate/cyclohexane 1:9 yielded the title compound as a colorless oil (6.5 g, 66%). R_f=0.31 (ethyl acetate/cyclohexane 2:8). ^{1}H NMR δ: 2.07 (quint., 2H, J=6.5 Hz); 2.75 (t, 2H, J=7 Hz); 3.55 (s, 2H); 3.57 (t, 2H, J=6.5 Hz); 3.73 (s, 3H). ^{13}C NMR δ: 23.4; 39.2; 43.8; 48.5; 51.8; 167.1; 201.4. IR (neat) ν_{max} 1740, 1710 cm^{-1}. Anal. calcd for $C_7H_{11}ClO_3$: C, 47.07; H, 6.21. Found: C, 47.01; H, 6.33.

4.1.2. [1-(1-(*S*)-Phenyl-ethyl)-pyrrolidin-2-ylidene]-acetic acid methyl ester (1a). To a mixture of methyl 6-chloro-3-oxohexanoate (1.4 g, 7.55 mmol) and (*S*)-1-phenylethylamine (1 mL, 7.55 mmol) was added a crystal of iodine, Na_2HPO_4 (1.1 g, 7.55 mmol) and Na_2SO_4 (1.1 g, 7.55 mmol). The reaction mixture was heated at 65°C for 90 h. After cooling to room temperature, CH_2Cl_2 (100 mL) was added and the organic layer was washed with water (35 mL). The aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layer was then extracted with 2N aqueous HCl solution (3×30 mL). The latter aqueous combined layer was basified by careful addition of solid K_2CO_3 and then extracted with CH_2Cl_2 (3×30 mL) The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Column chromatography eluted with ethyl acetate/cyclohexane 2:8 afforded the title compound (1.1 g, 60%) as a white solid. R_f=0.2 (ethyl acetate/cyclohexane 2:8). Spectroscopic data are in total agreement with those reported in the literature.[1]

4.1.3. [2-Hydroxy-1-(*S*)-phenyl-ethyl)-pyrrolidin-2-ylidene]-acetic acid methyl ester (1b). The title compound was obtained following a procedure similar to the one described for compound **1a**, using (*S*)-phenylglycinol as the amine. Column chromatography of the crude mixture eluted with ethyl acetate/cyclohexane 4:6 afforded compound **1b** (57%) as a solid. R_f=0.4 (ethyl acetate/cyclohexane 8:2). Spectroscopic data in total agreement with those reported in the literature.[1]

4.1.4. Methyl-6-chloro-3-oxoheptanoate. The title compound was prepared in a manner similar to that described for the hexanoate analogue, using 1-bromo-2-chloropropane as the alkylating agent. Column chromatography of the crude product using ethyl acetate/cyclohexane 1:9 as the eluent afforded the expected compound (7.5 g, 71%) as a colourless oil. ^{1}H NMR δ: 1.72–1.82 (m, 4H); 2.60 (t, 2H, J=7 Hz); 3.46 (s, 2H); 3.54 (t, 2H, J=7 Hz); 3.74 (s, 3H). ^{13}C NMR δ: 20.5; 31.5; 41.8; 44.5; 48.8; 52.2; 167.5; 202.0. IR (neat) ν_{max} 3500, 1750, 1720, 1630 cm^{-1}. Anal. calcd for $C_8H_{13}ClO_3$: C, 49.88; H, 6.80. Found: C, 49.92; H, 6.93.

4.1.5. [2-(4-Chlorobutyl)-[1,3]dioxolan-2-yl]-acetic acid methyl ester (7). A mixture of methyl-6-chloro-3-oxoheptanoate (2 g, 10.4 mmol), methyl orthoformate (3.45 mL, 20 mmol), ethyleneglycol (2.9 mL, 52 mmol) and *p*-TSA (0.19 g, 1 mmol) was stirred at room temperature for 6 h. Then a 5% aqueous solution of NaH_2PO_4 (3 mL) was added and the reaction mixture was stirred for 15 min. Et_2O (100 mL) was then added and the organic layer was washed twice with water (25 mL) and brine (25 mL) then dried over Na_2SO_4 and concentrated in vacuo. Column chromatography eluted with ethyl acetate/cyclohexane 2:8 afforded the title compound (2.1 g, 82%). R_f=0.3 (ethyl acetate/cyclohexane 2:8).^{1}H NMR δ: 1.51–1.62 (m, 2H); 1.75–1.88 (m, 4H); 2.66 (s, 2H); 3.54 (t, 2H, J=6.5 Hz); 3.70 (s, 3H); 3.96–4.02 (m, 4H). ^{13}C NMR δ: 20.7; 32.4; 36.6; 42.3; 44.7; 51.6; 65.0; 108.9; 169.8. IR (neat) ν_{max} 1735 cm^{-1}. Anal. calcd for $C_{10}H_{17}ClO_4$: C, 50.74; H, 7.24. Found: C, 50.62; H, 7.36.

4.1.6. {2-[4-(1-(*S*)-Phenylethylamino)-butyl]-[1,3]dioxolan-2-yl}acetic acid methyl ester (8a). To a solution of **7** (0.76 g, 3.2 mmol) in acetonitrile (50 mL) was added NaI (0.482 g, 3.2 mmol), Na_2CO_3 (1.7 g, 16 mmol), tetrabutylammonium iodide (0.118 g, 0.3 mmol) and (*S*)-1-phenylethylamine (0.389 g, 3.2 mmol). The reaction mixture was heated under reflux for 48 h, then allowed to cool to room temperature. Evaporation of the solvent was followed by extraction of the residue with Et_2O (3×25 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo to afford the title compound (1 g, 97%) as an oil. Due to the instability of this compound on silica gel, it was not further purified but the crude product was pure enough to be directly engaged in the next step. ^{1}H NMR δ: 1.30–1.54 (m, 4H); 1.38 (d, 3H, J=6.5 Hz); 1.74–1.81 (m, 2H); 2.37–2.60 (m, 2H); 2.64 (s, 2H); 3.68 (s, 3H), 3.78 (q, 1H, J=6.5 Hz); 3.92–3.99 (m, 4H); 7.22–7.35 (m, 5H). ^{13}C NMR δ: 21.3; 24.4; 30.0; 37.5; 42.5; 47.6; 51.8; 58.5; 65.2; 109.3; 126.7; 127.0; 128.5; 148.8; 170.0. IR (neat) ν_{max} 3400 (w), 1740 cm^{-1}. HRMS (CI) calcd for $C_{18}H_{28}NO_4$ (MH^+): 322.2018. Found: 322.2021.

4.1.7. {2-[4-(2-Hydroxy-1-(*S*)-phenylethylamino)-butyl]-[1,3]dioxolan-2-yl}acetic acid methyl ester (8b). The title compound **8b** was obtained as an oil (1.02 g, 95%) in a manner similar to the one described for **8a** using (*S*)-phenylglycinol as the amine. Due to the instability of this compound on silica gel, it was not further purified but the

crude product was pure enough to be directly engaged in the next step. ^{1}H NMR δ: 1.41–1.50 (m, 4H); 1.75–1.79 (m, 2H); 2.49–2.60 (m, 2H); 2.64 (s, 2H); 3.48–3.56 (m, 1H); 3.67 (s, 3H); 3.67–3.77 (m, 2H); 3.92–3.99 (m, 4H); 7.25–7.38 (m, 5H). ^{13}C NMR δ: 21.1; 30.0; 37.4; 42.4; 47.1; 51.8; 64.6; 65.1; 66.5; 109.2; 127.2; 127.6; 128.7; 140.7; 170.0. IR (neat) ν_{max} 3400, 1730 cm^{-1}. HRMS (CI) calcd for $C_{18}H_{28}NO_5$ (MH^+): 338.1967. Found: 338.1971.

4.1.8. [1-(1-(*S*)-Phenyl-ethyl)-piperidin-2-ylidene]-acetic acid methyl ester (3a). To a cooled solution of compound **8a** (119 mg, 0.37 mmol) in CH_2Cl_2 (30 mL) at 0°C was added drop wise BF_3–Et_2O (0.45 mL, 3.7 mmol). The reaction mixture was stirred at this temperature for 15 h then quenched with saturated $NaHCO_3$ aqueous solution (15 mL). The reaction mixture was allowed to warm to room temperature, then extracted with CH_2Cl_2 (4×15 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Column chromatography eluted with ethyl acetate/cyclohexane 2:8 afforded the title compound **3a** (96 mg, 74%) as a white solid. R_f=0.3 (ethyl acetate/cyclohexane 2:8). Spectroscopic data are in total agreement with those reported in the literature.[1]

4.1.9. 6-(1-(*S*)-Phenyl-ethylamino)-hexan-2-one (9). Compound **3a** (101 mg, 0.4 mmol) was stirred in 1N HCl aqueous solution (15 mL) for 15 h at room temperature. The reaction mixture was basified by careful addition of solid Na_2CO_3 and extracted with CH_2Cl_2 (3×15 mL). The combined organic layer was washed with brine (20 mL) dried over Na_2SO_4 and concentrated in vacuo yielding the title compound (72 mg, 85%). Due to the instability of this compound on silica gel, it was not further purified. ^{1}H NMR δ: 1.34 (d, 3H, J=6.5 Hz); 1.40–1.63 (m, 4H); 2.11 (s, 3H); 2.36–2.52 (m, 4H); 3.74 (q, 1H, J=6.5 Hz); 7.20–7.34 (m, 5H). ^{13}C NMR δ: 21.2; 23.0; 28.2; 29.9; 43.2; 46.7; 58.5; 127.0; 127.6; 128.7; 142.6; 208.8. IR (neat) ν_{max} 3320 (w), 1710 cm^{-1}.

4.1.10. 8a-Methyl-3-(*S*)-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine (10). The title compound **10** (153 mg, 67%) was obtained as an inseparable 9:1 diastereomeric mixture in manner similar to the one described for **3a**, starting from compound **8b** (279 mg, 8 mmol). R_f=0.3 (ethyl acetate/cyclohexane 2:8). Spectroscopic data are in total agreement with those reported in the literature.[1]

4.1.11. 8a-Methyl-3-(*S*)-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine (11). Compound **10** (109 mg, 0.4 mmol) was stirred in 1N HCl aqueous solution (15 mL) for 15 h at room temperature. The reaction mixture was basified by careful addition of solid Na_2CO_3 and extracted with CH_2Cl_2 (3×15 mL). The combined organic layer was washed with brine (20 mL) dried over Na_2SO_4 and concentrated in vacuo. Column chromatography eluted with ethyl acetate/cyclohexane 2:8 yielded the title compound (82 mg, 95%) as an inseparable 9:1 mixture of diastereomers. R_f=0.3 (ethyl acetate/cyclohexane 2:8). The spectroscopic data of the major one is in total agreement with those reported for the compound with a *cis* relationship between the phenyl and the methyl substituents.[13] Selected data for the minor *trans* isomer: ^{1}H NMR δ: 1.19 (s, 3H); 1.40–1.80 (m, 5H); 1.84–1.93 (m, 1H), 2.22–2.35 (m, 1H); 2.54–2.63 (m, 1H); 3.60 (dd, 1H, J=7.8 and 7.5 Hz); 3.90 (t, 1H, J=7.5 Hz); 4.18 (t, 1H, J=7.8 Hz); 7.25–7.41 (m, 5H). ^{13}C NMR δ: 13.8; 22.0; 25.5; 36.9; 43.1; 62.6; 71.9; 93.2; 127.6; 127.8; 128.5; 140.5.

4.1.12. (2*S*)-[1-(2-Hydroxy-1-(*S*)-phenyl-ethyl)-pyrrolidin-2-yl]-acetic acid methyl ester (12). Compound **1b** (90 mg, 0.34 mmol) in methyl acetate (10 mL) was subjected to hydrogenation (1 atm) in the presence of PtO_2 (18 mg) at room temperature for 24 h. The mixture was then filtered over a Celite® pad and the solvent was evaporated in vacuo yielding the title compound (91 mg, 99%) as a 95:5 diastereomeric mixture. Crystallization from cyclohexane afforded the pure major isomer (47 mg, 53%) as colorless crystals. R_f=0.4 (ethyl acetate/cyclohexane 8:2). ^{1}H NMR δ: 1.51–1.76 (m, 5H); 2.12–2.38 (m, 2H); 2.73–2.79 (m, 1H); 2.96–3.02 (m, 1H); 3.37–3.41 (m, 1H); 3.62 (s, 3H); 3.72–3.97 (m, 3H); 7.26–7.39 (m, 5H). ^{13}C NMR δ: 23.1; 30.8; 40.0; 51.5; 52.0; 56.6; 63.6; 67.8; 127.8; 128.5; 128.7; 139.2; 172.7. $[\alpha]_D^{20}$=+11 (c 1.09, $CHCl_3$). Mp 68°C. IR ($CHBr_3$) ν_{max} 3400, 1730 cm^{-1}. Anal. calcd for $C_{15}H_{21}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.07; H, 7.39; N, 5.29.

4.1.13. (2*S*)-Pyrrolidine-2-yl-acetic acid methyl ester (13). Compound **12** (0.6 g, 2.27 mmol) in methanol (30 mL) was subjected to hydrogenation (1 atm) in the presence of $Pd(OH)_2$/C (0.3 g) at room temperature for 1 h. The mixture was then filtered over a Celite® pad and the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and the organic layer was extracted with 2N aqueous HCl solution (2×25 mL). The combined aqueous layer was basified by careful addition of solid K_2CO_3 and extracted with CH_2Cl_2 (3×25 mL) The combined organic layer was washed with brine (20 mL) and dried over Na_2SO_4. Evaporation of the solvent in vacuo afforded the title compound (0.23 g, 70%) as an oil whose spectroscopic data are consistent with those reported in the literature.[18]

4.1.14. (2*S*)-[1-(2-Hydroxy-1-(*S*)-phenyl-ethyl)-piperidin-2-yl]-acetic acid methyl ester (14). A solution of $NaBH(OAc)_3$ was prepared by adding $NaBH_4$ (1.6 g, 42 mmol)) to glacial acetic acid (23.8 mL, 420 mmol)) while keeping the temperature between 10 and 20°C. After the hydrogen evolution ceased (30 min), acetonitrile (30 mL) was added and the solution was cooled to 0°C. Compound **10** (2.32 g, 8.4 mmol) was added in one portion and the reaction was stirred for 4 h at 0°C then at room temperature for 48 h. The solvents were evaporated in vacuo and the residue dissolved in CH_2Cl_2. The organic layer was neutralized with saturated aqueous Na_2CO_3 solution, dried over Na_2SO_4 and concentrated in vacuo. Column chromatography eluted with ethyl acetate/cyclohexane/NEt_3 2:8:0.3 yielded the title compound (2.16 g, 93%) as a 95:5 mixture of diastereomers. A second chromatography afforded the pure major diastereomer (1.45 g, 63%). R_f=0.26 (ethyl acetate/cyclohexane/NEt_3 2:8:0.3). ^{1}H NMR δ: 1.45–1.53 (m, 5H); 1.68–1.76 (m, 1H); 2.36–2.57 (m, 4H); 2.65–2.73 (m, 1H); 3.56–3.70 (m, 2H); 3.65 (s, 3H); 3.75–3.82 (m, 2H); 7.24–7.34 (m, 5H). ^{13}C NMR δ: 19.4; 25.8; 29.6; 32.0; 42.9; 51.6; 54.7; 62.2; 68.3; 127.7; 128.5; 128.6; 139.9; 173.4. $[\alpha]_D^{20}$=+73 (c 1.075, $CHCl_3$). IR

(neat) ν_{max} 3430, 1725 cm^{-1}. Anal. calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.35; N, 5.05. Found: C, 69.35; H, 8.29; N, 5.10.

4.1.15. (2*S*)-Methoxycarbonylmethylpiperidin-1-carboxylic acid *tert*-butyl ester (16). The major isomer **14** (0.23 g, 0.83 mmol) in methanol (15 mL) was subjected to hydrogenation 1 atm) in the presence of $Pd(OH)_2/C$ (0.11 g) at room temperature for 4 h. The mixture was then filtered over a Celite® pad and the solvent removed in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL). NEt_3 (1.15 mL, 8.3 mmol) and Boc_2O (0.4 g, 1.83 mmol) were successively added. The reaction mixture was stirred at room temperature for 15 h, then washed successively with 1N HCl aqueous solution (2×10 mL), saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL). Drying over Na_2SO_4 and concentration in vacuo was followed by column chromatography eluted with ethyl acetate/cyclohexane 3:7 to yield the title compound (0.19 g, 90%) as colourless oil. R_f=0.29 (ethyl acetate/cyclohexane 2:8). Spectroscopic data are in total agreement with those reported in the literature.[20] $[\alpha]_D^{20}$=−8.1 (*c* 3.615, $CHCl_3$) {lit.,[20] $[\alpha]_D^{20}$=−8.3 (*c* 4.54, $CHCl_3$) for the 2(*S*) enantiomer}.

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