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A β,β′-ketoaminoester as a valuable tool for the asymmetric construction of substituted homopipecolic esters: application to a formal synthesis of (+)-Calvine

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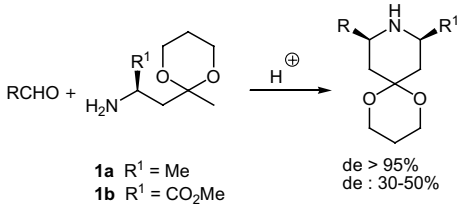
Abstract—A highly diastereoselective 1,4-addition involving Davies' lithium amide is employed as the key reaction to prepare, in five steps from ethyl acetoacetate, an enantiomerically pure keto protected β,β′-ketoaminoester. This latter was reacted with aldehydes in an intramolecular Mannich process and furnished a direct and stereoselective access to substituted homopipecolates. The validity of this approach was achieved through a new formal asymmetric synthesis of alkaloid (+)-Calvine.

1. Introduction

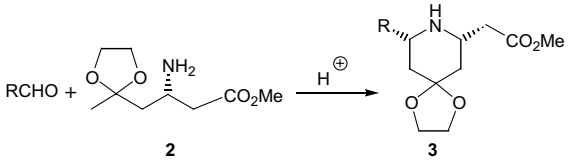
In previous work[1,2] we have described an efficient and stereoselective pathway to polysubstituted piperidine systems. Our approach, summarized in Scheme 1, rests on the use of an aldehyde involved in a Mannich-type reaction with an α-chiral ketoprotected 1,3-aminoketone and gives a selective access to the corresponding *cis*-2,6-disubstituted piperidines. Although having proven its efficiency through the concise total asymmetric synthesis of 2,6-disubstituted[3] and 2,4,6-trisubstituted[4] piperidine alkaloids, this strategy has found some limits in terms of generality.

Indeed, it implies the systematic enantioselective preparation of amines **1**, which remains sometimes difficult on a preparative scale, and gives variable diastereoselectivities depending on the nature of the α-amino substituent. As illustrated in Scheme 1, an alkyl group in **1a** furnishes the *cis*-2,6 adducts almost exclusively,[2] while the use of α-aminoacid derivative **1b** is accompanied by an obvious loss of selectivity.[5] Such results prompted us to focus our attention on chiral β-aminoester **2**, which according to our synthetic scheme, should permit highly stereoselective access to *cis*-2,6-disubstituted homopipecolic esters[2] **3** (Scheme 2).



Scheme 1. Synthesis of piperidines.

Homopipecolic acid derivatives may be considered as attractive target compounds. Effectively, these ring constrained β-aminoacids have been incorporated in peptides of pharmaceutical interest[6] in order to increase their bioactivity. Furthermore, they were described as valuable synthons for the stereoselective synthesis of alkaloids[7] as well as piperidine intermediates of bicyclic β-lactams[8] (carbacephams) of biological interest. Possessing different convertible functional groups allowing



Scheme 2. Synthesis of *cis*-2,6-disubstituted homopipecolic esters **3**.

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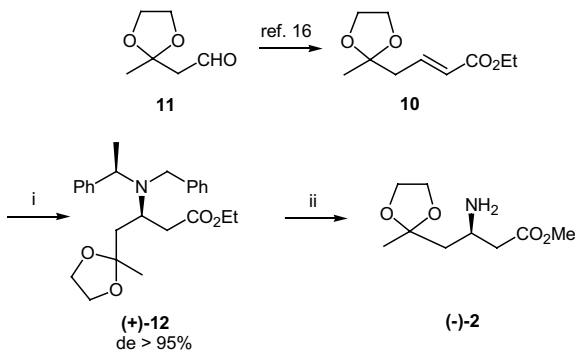
a wide range of selective transformations, we thought that compounds **3** exhibit a certain potential particularly in the field of the asymmetric synthesis of piperidine-containing structures. Thus, the preparation of homochiral β-aminoester **2** was studied.

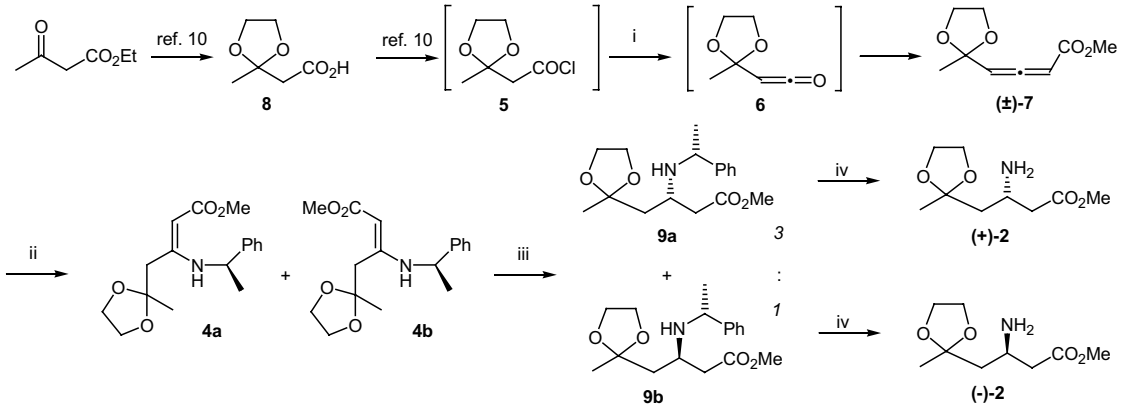
2. Results and discussion

Among the various synthetic strategies[9] permitting stereoselective access to β-aminoacids and esters, two were explored. The first one used as the key step the diastereoselective reduction of β-aminoester **4** bearing a chiral amino group, which was prepared as follows (Scheme 3). In situ treatment of acylchloride **5**, conveniently obtained in three steps from ethyl acetoacetate as described,[10] using triethylamine and methyl triphenylphosphoranylidene acetate at 20 °C in dichloromethane gave the reactive ketene intermediate **6**, then the desired Wittig adduct **7** (65% overall yield from acid **8**). This conjugated allenic ester **7** was then submitted to nucleophilic attack by (+)-(*R*)-α-methylbenzylamine in toluene under reflux. These conditions provided an inseparable 3:1 mixture of chiral enaminoesters **4a** and **4b** in 88% yield. As expected for such an addition of primary amine on allenic ester,[11,12] the *Z* stereoisomer **4a**, stabilized by an intramolecular H-bond, formed predominantly. Next was the reduction of the olefinic bond. Classical catalytic hydrogenation using 10% Pd/C[13] gave no reaction while treatment of the 3:1 **4a** and **b** mixture with sodium borohydride at room temperature in dichloromethane in the presence of zinc iodide[14] furnished the desired aminoesters **9a** and **9b** (3:1), albeit in moderate yield (42%). The optimal results were then obtained using in situ prepared sodium acetoxyborohydride, at 0 °C in AcOH/MeCN.[15] By this way, reduction of the 3:1 **4a** and **b** β-enaminoesters mixture yielded (81%) reduced analogues **9a** and **9b** (3:1, NMR of the crude), which were nicely separated by column chromatography ($\Delta R_f \sim 0.1$ in AcOEt). At this stage, the relative configurations of **9a** and **b** (Scheme 4) are given arbitrarily and will be confirmed later (vide infra). Finally, separated hydrogenolysis of **9a** and **9b** using methanolic ammonium formate in the presence of 10% Pd/C led to target β-aminoesters (+)-**2** $\{[\alpha]_D = 12.8\}$ and (−)-**2** $\{[\alpha]_D = -13.0\}$ in nearly quantitative yields. However, this synthesis was not satisfactory enough in regard to the restrained (50%) diastereoisomeric excess observed for **9a** and **b**. Accordingly, a second pathway to homochiral **2** was studied, involving as the key step the asymmetric Davies' lithium amide 1,4-addition on the required unsaturated ester **10** (Scheme 4). Thus, ester **10** was easily prepared, as reported,[16] by Wittig homologation of aldehyde **11**, which is readily available from ethyl acetoacetate after keto-protection then DIBAL-H reduction.[17] Treatment of **10** with lithium (*R*)-(−)-*N*-benzylphenylethylamide, at low temperature in THF, afforded β-aminoester (+)-**12** as almost a single isomer (91%, de >95%, from NMR datas).

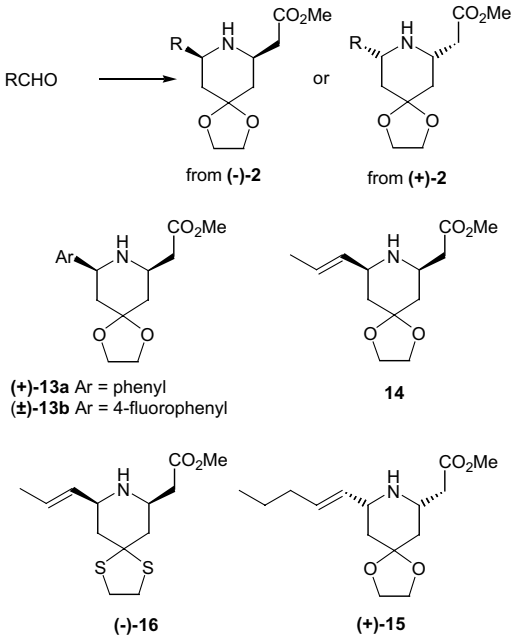


Scheme 4. Reagents and conditions: (i) *n*BuLi, (*R*)-*N*-benzylphenylethylamine, THF, −78 °C, 2 h, 91%; (ii) HCO_2NH_4, $Pd(OH)_2$/C, MeOH, reflux, 5 h, 94%.

The (*R*)-configuration of the created stereogenic center was given in respect with stereochemical behaviour of Davies' process.[18] Finally, hydrogenolysis of the benzyl groups, realized with ammonium formate in the presence of Pearlman's catalyst in refluxing methanol, gave completely transesterified β-aminoester (*R*)-(−)-**2** in 95% yield. The specific rotation of (−)-**2** $\{[\alpha]_D = -13.0\}$ was in perfect agreement with those obtained previously (vide supra). A further part of our program consisted of the valuation of compound **2** for the asymmetric preparation of *cis*-2,6-disubstituted-4-piperidones using our



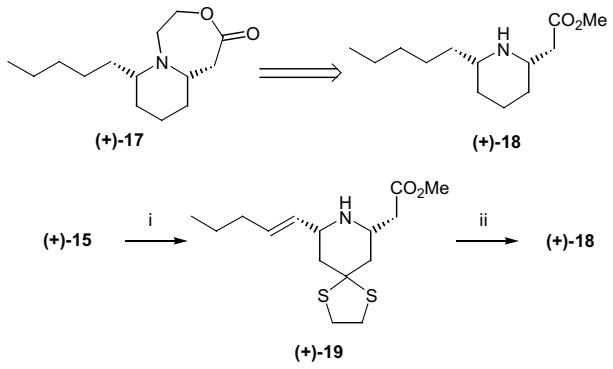
Scheme 3. Reagents and conditions: (i) NEt_3, Ph_3PCHCO_2Me, CH_2Cl_2, rt, 2 h, 65% from **8**; (ii) (+)-(*R*)-α-methylbenzylamine, toluene, reflux, 24 h, 88%; (iii) $NaHB(OAc)_3$, AcOH/MeCN, 0 °C, 4 h, 81%; (iv) HCO_2NH_4, Pd/C, MeOH, reflux, 5 h, 94%.



Scheme 5. Diastereoselective synthesis of methyl homopipecolates derivatives.

strategy[2] (Scheme 2). Thus, reaction of benzaldehyde, 4-fluorobenzaldehyde, crotonaldehyde and 2-hexenal with amine (+)-**2** or (−)-**2** in refluxing dichloromethane in the presence of magnesium sulfate as drying agent led (TLC monitoring), in approximatively 2 h, to the corresponding imines. These unstable intermediates were directly treated for 3 h with 1.3 equiv of *p*-toluene sulfonic acid (previously dried under Dean–Stark conditions) at 70 °C in toluene. Under these conditions, functionalized piperidones (+)-**13a** (65%), (±)-**13b** [80% from (±)-**2**], **14** and **(+)-15** (62%) were obtained (Scheme 5). Crude compound **14**, accompanied with a non negligible amount of the parent keto deprotected product was directly transformed into (−)-**16** under classical dithioketalization conditions (59% yield from (−)-**2**). In all cases, as observed with amine bearing an α-methyl group and contrarily with the use of an α-aminoester (Scheme 1), the *cis*-2,6-diastereoisomer was exclusively formed. Relative configurations of compounds **13**, **15** and **16** were unambigously established from ^{1}H NMR data, particularly with the signals corresponding to axial H-3 and axial H-5, showing typical coupling constants for a 2,6-diequatorial disubstitution in a chair conformation. The last points to be verified were the enantiomeric excesses of these new methyl homopipecolates together with the confirmation of the presumed absolute configurations. This was achieved through a formal synthesis of alkaloid (+)-Calvine **17**.

Piperidinic lactone (+)-Calvine **17** has recently been isolated[19] from the ladybird beetles of *Genus Calvia (Coccinellidae)* and fully characterized[20] by Braeckmann et al. who were able propose the first two unique enantioselective syntheses of **17**.[20] Their efficient strategy, based on the CN (*R*,*S*) methodology,[21] used aminoester (+)-**18** as the key intermediate (Scheme 6). As



Scheme 6. Reagents and conditions: (i) ethanedithiol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 85%; (ii) Raney Ni, MeOH, Δ, 88%.

shown in Scheme 6, we have considered that (+)-**18**, of already known absolute configurations, should be easily prepared by simple deoxygenation then olefinic reduction of piperidine (+)-**15**. Accordingly, (+)-**15** treated with ethanedithiol in the presence of $BF_3{\cdot}Et_2O$ in excess at room temperature in dichloromethane furnished the parent dithiolane derivative (+)-**19**, which when submitted to W_2 Raney nickel[22] in methanol under reflux, gave the expected piperidine (+)-**18** [72% yield from (+)-**15**]. The specific rotation of (+)-**18** $\{[\alpha]_D = 23.3$, (*c* 0.53 in $CHCl_3)\}$ was in agreement with those reported {lit.[20] $[\alpha]_D = 23.0$, (*c* 0.52 in $CHCl_3)\}$, as spectroscopic data. This confirmed that we were able to prepare homochiral (+)-(2*S*,6*S*)-**18** from the (+)-**2** synthon. Thus, we can assume that no racemization, due to retro-Michael nor retro-Mannich process occurred during the sequence, and consequently that our synthetic β-aminoesters (+)-**2** and (−)-**2** were enantiopure compounds of (*S*)- and (*R*)-configuration, respectively.

3. Conclusion

We have reported herein a short and efficient[23] asymmetric preparation of the ketoprotected β,β′-ketoaminoester **2** in five steps from ethyl acetoacetate. Through, notably, a new formal synthesis of alkaloid (+)-Calvine **17**, we could demonstrate that this synthon constitutes a valuable tool for the stereoselective synthesis of 2,4,6-functionalized homopipecolic esters, compounds of high synthetic potential. Exploitation of this strategy, in the field of enantioselective synthesis of piperidine-containing alkaloids as well as the asymmetric preparation of polysubstituted bicyclic β-lactams (carbacephams) of biological interest is currently in progress.

4. Experimental

4.1. General

Unless otherwise specified, reagents were obtained from commercial suppliers. Solvents were dried and freshly distilled following the usual procedures. Organic product solutions were dried over sodium sulfate prior to evaporation of the solvents under reduced pressure on a

rotatory evaporator. Thin layer chomatography was performed on TLC precoated aluminium backed silica plates and spots visualized using UV light (254 nm) before using ethanolic phosphomolybdic acid solution (heating). Column chromatography was carried out on silica gel (70–230 mesh). ^{1}H and ^{13}C NMR spectra were measured at 400.13 and 100.61 MHz, respectively. Chemicals shifts are reported in ppm relative to $SiMe_4$. Signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), br (broad) and coupling constant (J) values given in Hz. Infrared spectra were recorded on a FTIR spectrophotometer. Electron Impact Hight Resolution Mass Spectra (EI-HRMS) were obtained from the Centre Régional de Mesures Physiques de l'Ouest, Universitéde Rennes I, France. Optical rotations were measured at 589 nm and specific rotations are given in units of 10^{-1}deg cm^2 g^{-1}.

4.1.1. (±)-Methyl 5,5-ethylenedioxy-hexa-2,3-dienoate 7. To a cold (0 °C) stirred solution of crude ketoprotected ketoacid **8** (1.5 g, 10.3 mmol) in dichloromethane (20 mL) was added, under argon, 6.2 mL of a 2 M oxalylchloride solution in dichloromethane (12.4 mmol). The resulting mixture was stirred at room temperature for 3 h then transferred via cannula to a solution of triethylamine (2.86 mL, 20.6 mmol) and methyltriphenylphosphoranylidene acetate (3.44 g, 10.3 mmol) in dichloromethane (100 mL). After 2 h of stirring, the solvent was evaporated and the residue directly purified by column chromatography (ethyl acetate/cyclohexane, 1:5) to give 1.23 g (65%) of allenic ester (±)-**7** as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (1H, d, $J = 6.0$ Hz), 5.62 (1H, d, $J = 6.0$ Hz), 4.09-3.95 (4H, m), 3.75 (3H, s), 1.59 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.9, 165.7, 106.3, 99.0, 90.6, 65.0, 64.5, 52.1, 25.3; IR (neat) 1965, 1720, 1376, 1268, 1034, 870, 803 cm^{-1}.

4.1.2. Methyl 5,5-ethylenedioxy-3-(1′-methylbenzylamino)-hex-2-enoate 4. To a stirred solution of allenic compound **7** (3.0 g, 16 mmol) in toluene (100 mL) under argon was added a solution of (+)-(*R*)-α-methylbenzylamine (1.88 mL, 14.7 mmol) in toluene (30 mL). The resulting mixture was refluxed for 24 h. After cooling at room temperature, the solvent was eliminated in vacuo. Column chromatography (diethyl ether/cyclohexane, 1:3) afforded 4.39 g of an 3:1 unseparable mixture of enaminoesters **4a** and **4b** as a yellow oil (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (0.75H, br d, $J = 7.0$ Hz), 7.38–7.20 (5H, m), 5.62 (0.25H, br s), 4.94 (0.75H, p, $J = 7.0$ Hz), 4.64 (0.75H, s), 4.55 (0.25H, s), 4.40 (0.25H, p, $J = 7.0$ Hz), 4.05–3.92 (4H, m), 3.68 (3×0.75H s), 3.55 (3×0.25H, s), 3.45 (0.25H, d, $J = 14.0$ Hz), 3.34 (0.25H, d, $J = 14.0$ Hz), 2.54 (0.75H, d, $J = 14.0$ Hz), 2.30 (0.75H, d, $J = 14.0$ Hz), 1.50 (3×0.75H, d, $J = 7.0$ Hz), 1.47 (3×0.25H, d, $J = 7.0$ Hz), 1.35 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 169.1, 160.1, 156.9, 145.3, 145.2, 128.8, 127.3, 127.0, 125.7, 125.6, 109.8, 109.0, 86.0, 85.3, 65.1, 64.8, 64.6, 64.5, 52.8, 52.6, 50.1, 42.0, 38.2, 25.3, 24.9, 23.9, 23.2; IR (neat) 3392, 3275, 1691, 1654, 1608, 1376, 1262, 1048, 786, 701 cm^{-1}; HRMS calcd for $C_{17}H_{23}NO_4$, 305.1627, found 305.1615.

4.1.3. Methyl 5,5-ethylenedioxy-3-(1′-methylbenzylamino)-hexanoate 9. Sodium borohydride (0.555 g, 14.7 mmol) was placed by small portions in 8.5 mL of acetic acid at room temperature under stirring. At the end of gaseous evolution, acetonitrile (8.5 mL) was added and the resulting solution cooled at 0 °C before addition of the 3:1 mixture of enaminoesters **4a** and **b** (1.5 g, 4.92 mmol) previously obtained. After 4 h of stirring at 0 °C, the solvents were evaporated and residue diluted with saturated aqueous solution of Na_2CO_3 (10 mL), dried, filtrated then concentrated. Column chromatography (EtOAc/cyclohexane, 1:1) gave 916 mg (61%) and 305 mg (20%) of respectively β-aminoesters **9a** and **9b** as colourless oil.

(+)-(1′*R*,3*S*)-**9a**: $[\alpha]_D^{20} = +14.1$ (c 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.19 (5H, m), 3.94–3.80 (5H, m), 3.60 (3H, s), 3.01 (1H, m), 2.50 (1H, dd, $J = 15.5$ and 5.5 Hz), 2.27 (1H, br s), 1.96 (1H, dd, $J = 14.5$ and 5.5 Hz), 1.77 (1H, dd, $J = 14.5$ and 7.0 Hz), 1.33 (3H, d, $J = 6.5$ Hz), 1.27 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 146.1, 128.3, 126.8, 109.6, 64.4, 64.3, 55.7, 51.3, 49.4, 42.5, 40.8, 24.7, 24.2; IR (neat) 3339, 1738, 1256, 1054, 892, 764, 703 cm^{-1}; HRMS calcd for $C_{17}H_{25}NO_4$, 307.1783, found 307.1784.

(+)-(1′*R*,3*R*)-**9b**: $[\alpha]_D^{20} = +44.7$ (c 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.20 (5H, m), 3.95-3.75 (5H, m), 3.66 (3H, s), 2.97 (1H, m), 2.56–2.42 (2H, m), 2.15 (1H, br s), 1.86–1.75 (2H, m), 1.36 (3H, d, $J = 6.5$ Hz), 1.11 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 145.9, 128.5, 126.4, 109.5, 64.4, 64.3, 55.9, 51.1, 49.4, 42.7, 40.5, 24.5, 24.1; IR (neat) 3339, 1738, 1256, 1054, 892, 764, 703 cm^{-1}; HRMS calcd for $C_{17}H_{25}NO_4$, 307.1783, found 307.1784.

4.1.4. (+)-(3*S*)-Methyl 3-amino-5,5-ethylenedioxyhexanoate 2. To a stirred suspension of 10% Pd/C (261 mg) in anhydrous methanol (20 mL) was added a solution of aminoester (+)-**9a** (1.00 g, 3.26 mmol) in methanol (30 mL) then ammonium formate (1.02 g, 16.30 mmol). The resulting mixture was heated at reflux for 5 h. After cooling at room temperature, the catalyst was removed by filtration on celite®. The residue obtained after evaporation of the solvent was diluted with 30 mL of dichloromethane. This organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with dichloromethane (3×30 mL) and the combined organic extracts dried, filtrated and then concentrated to afford 622 mg (94%) of pure enaminoester (+)-**2** as pale yellow oil. $[\alpha]_D^{20} = +12.3$ (c 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98–3.90 (4H, m), 3.67 (3H, s), 3.52–3.48 (1H, m), 2.49 (1H, dd, $J = 16.0$ and 5.0 Hz), 2.34 (1H, dd, $J = 16.0$ and 8.0 Hz), 1.83 (1H, br s), 1.77–1.73 (2H, m), 1.35 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 109.7, 64.6, 64.3, 51.5, 45.4, 4 4.6, 42.9, 24.6; IR (neat) 3377, 1735, 1438, 1379, 1255, 1042, 949, 816 cm^{-1}; HRMS calcd for $C_7H_{12}NO_3$ ($M-C_2H_5O$), 158.0817, found 158.0797.

4.1.5. (+)-(1′*R*,3*S*)-Ethyl-3-(*N*-benzyl-*N*-1′-ethylbenzylamino)-5,5-ethylenedioxyhexanoate 12. To a cold (0 °C) solution of (+)-(*R*)-*N*-benzyl-*N*-α-methyl benzylamine (3.37 g, 16.0 mmol) in dry THF (50 mL) was added slowly under argon 6.4 mL of a 1.6 M *n*-butyllithium solution in hexanes (15 mmol). The resultant pink solution of lithium amide was stirred for 15 min and then cooled at −78 °C before dropwise addition of a solution of conjugated ester **10** (2.00 g, 10 mmol) in 20 mL of dry THF. After 3 h stirring at −78 °C, a saturated aqueous solution of NH_4Cl (30 mL) was added dropwise and the resulting solution allowed to warm to room temperature. Aminoester **12** was then extracted with diethylether (4×30 mL). The combined organic extracts were dried, filtered and evaporated. Column chromatography using ethyl acetate:cyclohexane 1:7 as eluent furnished 3.73 g (91%) of (+)-**12** as a colourless oil. $[\alpha]_D^{20} = +8.2$ (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.00 (10H, m), 3.98-3.68 (7H, m), 3.64 (1H, d, $J = 14.5$ Hz), 3.55 (1H, d, $J = 14.5$ Hz), 3.42 (1H), m), 2.40 (1H, dd, $J = 14.0$ and 5.0 Hz), 2.26 (1H, dd, $J = 14.0$ and 8.5 Hz), 2.04 (1H, dd, $J = 14.5, 2.0$ Hz), 1.61 (1H, dd, $J = 14.5$ and 9.0 Hz), 1.29 (3H, d, $J = 7.0$ Hz), 1.21 (3H, s), 1.02 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 144.1, 141.4, 128.7, 128.3, 128.1, 127.8, 126.6, 109.8, 64.8, 64.5, 60.0, 57.5, 50.6, 50.1, 41.7, 39.8, 26.9, 25.0, 16.3, 14.1; IR (neat) 1732, 1373, 1046, 749, 700 cm^{-1}; EI-MS (70 eV) 411 (M^+, 3), 396 (12), 324 (35), 310 (24), 206 (32), 105 (53), 87 (100).

4.1.6. (−)-(3*R*)-Methyl-3-amino-5,5-ethylenedioxyhexanoate 2. Following the procedure described for synthesis of (+)-**2** from (+)-**9a**, using 20% $Pd(OH)_2$/C in place of 10% Pd/C, hydrogenolysis of (+)-**12** (2.05 g) afforded 954 mg (94%) of pure (−)-**2**. $[\alpha]_D^{20} = -13.0$ (*c* 1.50, $CHCl_3$). Other data were identical with those given for its enantiomer (vide supra).

4.2. Typical procedure for intramolecular Mannich-type cyclization

To a stirred solution of aldehyde (1.1 mmol) in dichloromethane (10 mL) was added $MgSO_4$ (ca 1 g) followed by a solution of aminoester (+) or (−)-**2** (1 mmol) in dichloromethane (5 mL). The resulting solution was heated at reflux until disappearance (TLC monitoring) of the amine (3-4 h) and then cooled to room temperature and transferred via a cannula to a solution of dry *p*-TsOH (1.3 mmol) in toluene (30 mL). The resulting mixture was heated at 70 °C for 3-4 h. After being cooled to room temperature, a saturated aqueous solution of $NaHCO_3$ (8 mL) was added and the ketoprotected piperidone extracted with ethylacetate (4×20 mL). The combined organic extracts were dried, filtered and evaporated. The residue was purified by column chromatography.

4.2.1. (+)-(2*S*,6*R*)-1-Aza-6-(methoxycarbonyl)methyl-2-phenyl-1′,3′-dioxaspiro[5,4]decane 13a. Following the cyclization procedure, benzaldehyde (117 mg) and amine (−)-**2** (203 mg) afforded cyclic β-aminoester (+)-**13a** as a yellow oil (189 mg, 65%). $[\alpha]_D^{20} = +28.0$ (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): δ 7.47 (2H, d, $J = 8.0$ Hz), 7.20 (3H, m), 4.22 (1H, dd, $J = 11.5$ and 3.0 Hz), 3.64 (5H, m), 3.34 (3H, s), 2.37 (1H, dd, $J = 16.0$ and 8.0 Hz), 2.32 (1H, dd, $J = 16.0$ and 5.0 Hz), 2.04 (1H, dt, $J = 12.0$ and 3.0 Hz), 2.00 (1H, br s), 1.96 (1H, t, $J = 12.5$ Hz), 1.87 (1H, dt, $J = 12.5$ and 2.5 Hz), 1.69 (1H, t, $J = 12.0$ Hz); ^{13}C NMR (100 MHz, C_6D_6): δ 172.5, 143.8, 128.5, 127.3, 126.9, 107.8, 64.5, 64.3, 58.6, 51.6, 51.0, 43.0, 41.0, 40.8; IR (neat) 3323, 1732, 1313, 1263, 1178, 1058, 760, 700 cm^{-1}; HRMS calcd for $C_{16}H_{21}NO_4$ 291.1471, found 291.1480.

4.2.2. (±)-(2*S,6*R**)-1-Aza-2-(4′-fluoro)phenyl-6-(methoxycarbonyl) methyl-1′,3′-dioxaspiro[5,4]decane 13b.** Following the cyclization procedure, 4-fluorobenzaldehyde (137 mg) and amine (±)-**2** (203 mg) afforded cyclic β-aminoester (±)-**13b** as a colourless oil (247 mg, 80%). ^{1}H NMR (400 MHz, $CHCl_3$): δ 7.34 (2H, m), 7.00 (2H, tt, $J = 9.0$ and 2 Hz), 3.96 (5H, m), 3.67 (3H, s), 3.36 (1H, m), 2.45 (2H, d, $J = 6.5$ Hz), 2.23 (1H, br. s), 1.82 (1H, dt, $J = 12.0$ and 2.5 Hz), 1.72 (1H, dt, $J = 12.0$ and 2.5 Hz), 1.68 (1H, t, $J = 12.0$ Hz), 1.51 (1H, t, $J = 12.0$ Hz); ^{13}C NMR (100 MHz, $CHCl_3$): δ 172.5, 162.0 ($J_{C-F} = 245$ Hz), 139.6, 128.3, 115.2 ($J_{C-F} = 20$ Hz), 107.7, 64.5, 64.3, 57.8, 50.9, 50.2, 43.2, 40.9, 40.6; IR (neat) 3321, 1739, 1605, 1509, 1315, 1224, 1061, 836 cm^{-1}; EI-MS (70 eV) 309 (M^+, 4), 264 (32), 236 (20), 208 (42), 150 (100), 122 (40), 87 (56).

4.2.3. (−)-(2*S*,6*S*)-1-Aza-6-(methoxycarbonyl)methyl-2-prop-1″-enyl-1′,3′-dithiaspiro[5,4]decane 16. Following the cyclization procedure, crotonaldehyde (150 mg) and amine (−)-**2** (406 mg) afforded crude cyclic β-aminoester **14** accompanied with the parent ketodeprotected compound. This mixture was directly submitted to dithioketalization conditions as follows. To a stirred solution of the mixture obtained in dichloromethane (20 mL) was added dropwise at room temperature, ethane dithiol (900 μL, 10 mmol) then $BF_3{\cdot}OEt_2$ (1.32 mL, 10 mmol). After 24 h of stirring, 20 mL of dichloromethane then 20 mL of 1 M aqueous NaOH were added before extraction with dichloromethane (4×20 mL). The combined organic phases were dried, filtered and evaporated. Purification by column chromatography (EtOAc/cyclohexane, 1:1) led to 339 mg (59%) of dithioderivative (−)-**16** as yellow oil. $[\alpha]_D^{20} = -17.2$ (*c* 1.45, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 5.55 (2H, m), 3.59 (1H, m), 3.49 (1H, m), 3.35 (3H, s), 2.88 (4H, s), 2.40–2.10 (5H, m), 2.02 (1H, dd, $J = 12.5$ and 11.0 Hz), 1.85 (1H, dd, $J = 12.5$ and 11.5 Hz), 1.57 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, C_6D_6): δ 172.4, 133.1, 126.5, 66.1, 57.9, 52.0, 51.6, 48.2, 47.8, 40.5, 39.2, 37.8, 17.8; IR (neat) 3328, 1733, 1672, 1436, 1200, 1174, 968 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO_2S_2$ 287.1014, found 287.1019.

4.2.4. (+)-(2*R*,6*S*)-1-Aza-6-(methoxycarbonyl)methyl-2-pent-1″-enyl-1′,3′-dioxaspiro[5,4]decane 15. Following the cyclization procedure, hex-2-enal (162 mg) and

amine (+)-**2** (300 mg) afforded β-aminoester (+)-**15** as a yellow oil (236 mg, 62%). $[\alpha]_D^{20} = +13.6$ (*c* 1.06, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.66–5.57 (1H, m), 5.37 (1H, dd, $J = 15.5$ and 7.0 Hz), 3.95 (4H, s), 3.68 (3H, s), 3.39–3.32 (1H, m), 3.28–3.20 (1H, m), 2.42 (2H, m), 2.07 (1H, br s), 2.00–1.65 (2H, m), 1.72–1.58 (2H, m), 1.43 (1H, t, $J = 12.0$ Hz), 0.88 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 132.2, 131.4, 107.6, 64.4, 64.2, 56.1, 51.6, 50.3, 41.3, 40.9, 40.7, 34.4, 22.3, 13.6; IR (neat) 3328, 1736, 1437, 1317, 1277, 1198, 1173, 970 cm^{-1}; HRMS calcd for $C_{15}H_{25}NO_4$, 283.1769 found 283.1784.

4.2.5. (+)-(2*R*,6*R*)-1-Aza-6-(methoxycarbonyl)methyl-2-pent-1″-enyl-1′,3′-dithiospiro[5,4]decane 19. To a stirred solution of cyclic aminoester (+)-**15** (200 mg, 0.71 mmol) in 10 mL of anhydrous dichloromethane was added dropwise at room temperature 300 μL (3.53 mmol) of ethanedithiol and 440 μL (3.53 mmol) of $BF_3{\cdot}OEt_2$. The resulting mixture was stirred for 24 h then diluted with dichloromethane (10 mL) before addition of 1 M aqueous NaOH (10 mL) then extraction with dichloromethane (3×15 mL). The combined organic extracts were dried, filtered and evaporated. Purification by column chromatography (ethylacetate/cyclohexane, 1:1) afforded dithioketal compound (+)-**19** as pale yellow oil (189 mg, 85%). $[\alpha]_D^{25} = +15.6$ (*c* 1.09, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.61 (1H, m), 5.35 (1H, dd, $J = 15.5$ and 7.0 Hz), 3.66 (3H, s), 3.36–3.25 (5H, m), 3.19 (1H, m), 2.40 (2H, m), 2.07 (1H, br s), 2.05–1.90 (4H, m), 1.78 (1H, t, $J = 12.0$ Hz), 1.73 (1H, t, $J = 12.0$ Hz), 1.41–1.29 (2H, m), 0.86 (3H, t, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 131.9, 131.8, 66.1, 58.0, 52.1, 51.7, 48.3, 47.8, 40.5, 39.2, 37.9, 34.4, 22.2, 13.7; IR (neat) 3328, 1736, 1437, 1317, 1277, 1173, 970 cm^{-1}; HRMS calcd for $C_{15}H_{25}NO_2S_2$315.1315, found 315.1327.

4.2.6. (+)-(2*S*,6*S*)-2-(Methoxycarbonyl)methyl-6-pentyl-piperidine 18. To a stirred solution of dithioketal (+)-**19** (140 mg, 0.44 mmol) in absolute methanol (5 mL) was added freshly prepared W_2 Raney nickel (ca 1 g). The resulting suspension was heated at reflux for 2 h then cooled to room temperature. The suspension was then filtered through celite® and the filtrate concentrated under reduced pressure. The residue was dissolved in 1 M aqueous NaOH and the piperidine extracted with dichloromethane (4×10 mL). The combined organic extracts were washed with brine and dried. Evaporation of the solvent followed by column chromatography (ethyl acetate/methanol, 9:1) gave piperidine (+)-**18** (89 mg, 88%) as colourless oil. $[\alpha]_D^{20} = +23.3$ (*c* 0.53, $CHCl_3$), lit.[20] $[\alpha]_D^{20} = +23.0$ (*c* 0.52, $CHCl_3$); Spectral data are identical with those reported.[20]

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