Tetrahedron 66 (2010) 8832–8836

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Application of asymmetric phase-transfer catalysis in the enantioselective synthesis of *cis*-5-substituted proline esters

Barry Lygo [a,*], Christopher Beynon [a], Michael C. McLeod [a], Claude-Eric Roy [a], Charles E. Wade [b]

[a] School of Chemistry, University of Nottingham, Nottingham NG7 2RD, UK
[b] GlaxoSmithKline, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK

ARTICLE INFO

Article history:
Received 23 July 2010
Received in revised form 2 September 2010
Accepted 20 September 2010
Available online 24 September 2010

Keywords:
Asymmetric catalysis
Michael addition
Hydrogenation
Amino acids
Pyrrolidines

ABSTRACT

A simple, highly stereoselective three-step sequence for the enantioselective synthesis of *cis*-5-substituted proline esters is described. This sequence features an asymmetric PTC Michael addition, followed by acid catalysed imine exchange and catalytic hydrogenation. Application of this chemistry in the synthesis of the nonpeptide cholecystokinin antagonist (+)-RP-66803 **11** is also described.

1. Introduction

Compounds incorporating the *cis*-2,5-disubstituted pyrrolidine fragment **1** have attracted great interest from synthetic organic chemists and this has resulted in the preparation and characterisation of a large number of molecules possessing this sub-structural element (Fig. 1).[1] Within this field of study, pyrrolidine **2** and indolizidine alkaloids **3**[2] have attracted particular attention due to their occurrence as signalling and protective agents in ants and amphibians.[3] 5-Substituted proline derivatives **4** have also proved to be of significant interest as modified peptide scaffolds,[4] as key fragments in potential pharmaceutical agents,[5,6] and as ligands for asymmetric catalysis.[7]

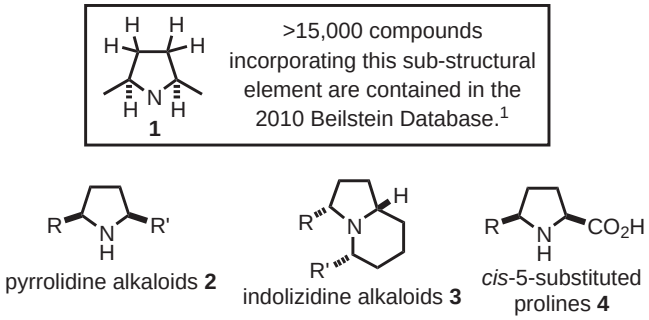


Fig. 1. 2,5-Disubstituted pyrrolidines.

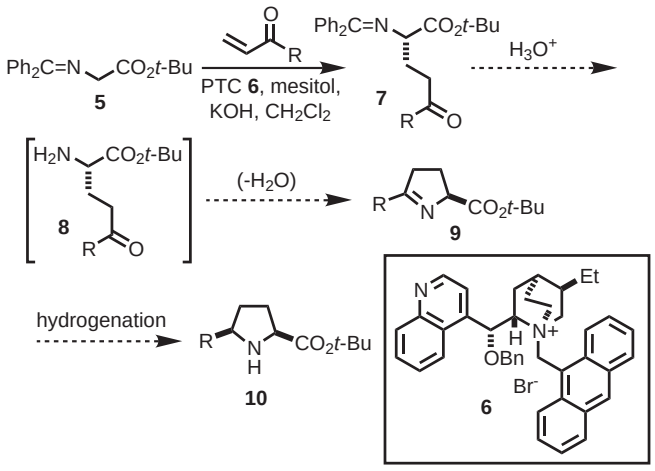
Single enantiomers of these structures are commonly prepared from pyroglutamic acid derivatives,[8] but in recent years there has been increasing interest on the development of alternative approaches that expand the range of structures, which can be accessed rapidly from simple starting materials.[9]

We recently demonstrated that the use of mesitol as a co-catalyst in conjunction with the readily-available cinchona alkaloid-derived phase-transfer catalyst **6**[10] allows for highly enantioselective addition of glycine imine **5** to a wide range of Michael acceptors.[11] If the Michael acceptor is an enone, this offers the possibility of preparing enantioenriched pyrrolidines **10** via the three-step sequence outlined in Scheme 1.[12]

This approach takes advantage of the fact that hydrolysis of the benzophenone imine moiety in the initial Michael adducts **7** should lead directly to the pyrroline intermediate **9**.[13] Subsequent hydrogenation would then be expected to favour formation of the *cis*-5-substituted proline ester **10**. Although this sequence appears straightforward, we envisaged two key issues that might limit application of this chemistry to the synthesis of highly enantioenriched products. Firstly, the pyrroline **9** may be vulnerable to racemisation during the hydrolysis step, especially if the R-substituent is a conjugating group. Secondly, competing hydrogenolysis of the C–N bond may be an issue during the hydrogenation step if R=aryl.[14]

* Corresponding author. E-mail address: b.lygo@nottingham.ac.uk (B. Lygo).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.09.075



Scheme 1. Three-step sequence to 5-substituted proline esters.

For these reasons, we initially chose to investigate application of this approach in the synthesis of (+)-RP-66803 **11**, a nonpeptide cholecystokinin antagonist Fig. 2.[5,15]

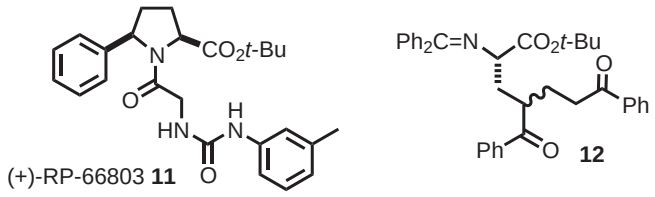
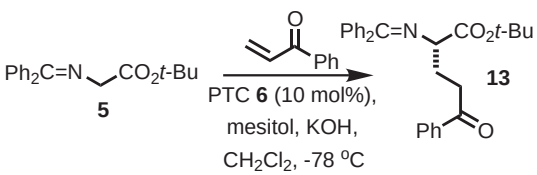


Fig. 2. Structures **11** and **12**.

2. Results and discussion

The first step of this synthesis required asymmetric conjugate addition of glycine imine **5** to phenylvinylketone (PVK). Using PTC **6**, under our standard conditions (Table 1, entry 1),[11] delivered the desired adduct **13** with high enantiomeric excess, but in relatively modest yield. Significant quantities of the di-addition product **12** were also produced in this reaction suggesting that the intermediate enolate was undergoing a second addition to PVK, a problem not observed with less reactive enones. Fortunately this could easily be circumvented simply by adding the PVK slowly over 2 h. This modification lowers the concentration of the PVK in the reaction mixture and delivers near quantitative yields of the monoadduct **13** (Table 1, entry 2). We briefly examined the effect of lowering the catalyst loading (Table 1, entries 3–4), but led to increased reaction times along with a lowering of both chemical yield and enantioselectivity.

Table 1
Enantioselective addition of imine **5** to PVK

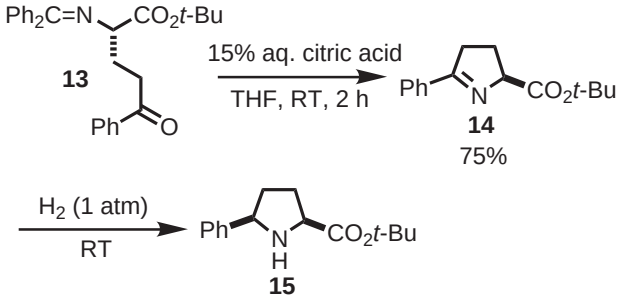


mol % PTC	Time (h)	Yield (%)	ee (%)
10	1.5	63	91
10[a]	2.5	99	89
5	3.0	49	92
5	11	51	86

[a] The enone was added over 2 h.

With adduct **13** in hand, we next examined the hydrolysis/cyclisation/hydrogenation sequence (Table 2). Conversion to pyrroline **14** was straightforward, and we were able to establish that no loss of stereochemical integrity occurred under the reaction conditions shown.[16] Prolonged reaction times (days) or the use of stronger acids (e.g., AcOH) did lead to partial racemisation of the product **14**.

Table 2
Formation of *cis*-5-phenyl proline *tert*-butyl ester **15**

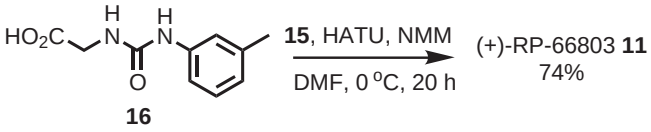


Hydrogenation conditions	Time (h)	Yield **15** (%)	dr[a]	ee[b]
10% Pd/C, MeOH	3	60[c]	>20:1	89
5% Pt/C, MeOH	3	87	>20:1	89
5% Pt/C, AcOH[d]	4	64	>20:1	73

[a] By ^{1}H NMR spectroscopy (the minor diastereoisomer could not be detected).
[b] Imine **13** used in this study was 89% ee.
[c] The hydrogenolysis product was also obtained in 30% yield.
[d] Imine **13** was used as the substrate.

Hydrogenation of pyrroline esters similar to **14** is typically performed using Pd/C or PtO_2.[6,7,9b,14,17] When applied to substrate **14**, hydrogenation using 10% Pd/C gave competing hydrogenolysis (e.g., Table 2 entry 1). Use of PtO_2 avoids this problem, but requires higher pressures of hydrogen in order to achieve a reasonable rate of reaction. So, in an effort to optimise the hydrogenation we screened a range of other hydrogenation catalysts (5% Pd/C, 5% Pt/C, 5% Rh/C, 1% Pt+2% V/C).

This study established that 5% Pt/C[18] gave the highest rate of hydrogenation, leading to complete reduction of pyrroline **14** within 3 h at atmospheric pressure (Table 2, entry 2). Using these conditions, the desired *cis*-5-substituted proline ester **15** was obtained as a single diastereoisomer. We were also able to confirm that no racemisation occurred under these reaction conditions.[16] All other catalysts investigated gave substantially lower rates of reaction. The use of 5% Pt/C to generate 5-substituted proline derivatives in this way has rarely been reported,[19] but these results suggest that it may warrant more widespread application. Attempts to promote imine exchange and hydrogenation in the same pot were partially successful (e.g., Table 2, entry 3), but this also led to partial racemisation, so the two-step sequence was preferred. Synthesis of (+)-RP-66083 **11** was then completed by coupling of pyrrolidine **15** with the known glycine derivative **16**[5] (Scheme 2).



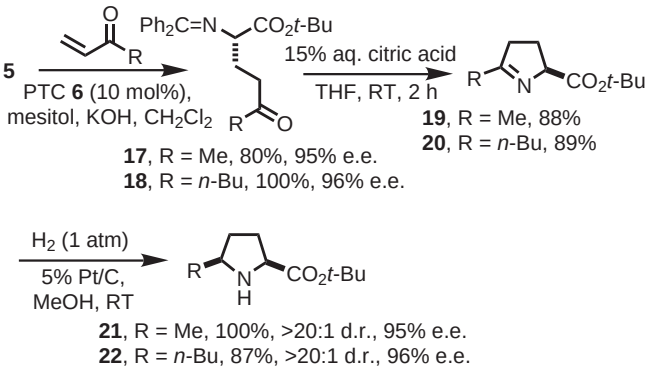
Scheme 2. Completion of the synthesis of (+)-RP-66803 **11**.

Material prepared in this way had spectroscopic properties in good agreement with those previously reported,[5] and the sign of optical rotation of the product **11** allowed us to confirm that the asymmetric PTC Michael addition outlined in Table 1 was selective for the (*S*)-enantiomer of the product **13**. This is in line with

expectations[11] and in agreement with stereochemical models developed for PTC alkylation reactions involving glycine imine **5** and catalyst **6**.[20]

As outlined earlier, pyrrolidine **15** was chosen as the initial target in an effort to develop a robust route from glycine imine **5** to proline ester derivatives **10**. It was anticipated that a route that was successful for this target should also work well for 5-alkyl-substituted proline esters. In order to confirm this is the case, we have also applied the same sequence to the synthesis of esters **21** and **22**. Ester **21** was selected as a target because it represents the simplest 5-substituted proline *tert*-butyl ester,[21] and **22** was selected because *cis*-5-*n*-butyl proline esters have been shown to be key intermediates for the synthesis of a range of pyrrolidine[22] and indolizidine alkaloids.[12,23]

The synthesis of both of these target structures proved straightforward (Scheme 3). In both cases it was not necessary to employ slow addition of the enone in order to achieve high yields in the asymmetric PTC Michael addition. This simply reflects the reduced reactivity of alkylvinylketones compared with PVK. High enantiomeric excess was observed for both adducts (**17** and **18**), and again we were able to confirm that this was preserved throughout the three-step sequence to the final product **22**.[16]



Scheme 3. Synthesis of 5-alkyl substituted proline esters.

This study also led to an important observation regarding the protocol for the asymmetric Michael addition leading to imine **18**. In our preliminary investigations this compound was only prepared on 0.17 mmol scale. On scaling up the process, it proved important to ensure that the temperature of the catalyst/mesitol mixture does not rise above 0 °C during the reaction with potassium hydroxide. This precaution results in significantly improved yield and enantiomeric excess compared with that previously reported[11] and has been successfully applied to the preparation of adduct **18** on 0.3–30 mmol scale.

3. Conclusion

In conclusion, we have been able to develop an efficient, robust three-step sequence for the stereoselective synthesis of *cis*-5-substituted proline esters. The sequence described employs catalysis in all three steps and generates the final products in high enantio- and diastereo-selectivity.

4. Experimental

4.1. General information

All solvents and chemicals were used as provided by the supplier. Reactions were monitored by thin layer chromatography using Merck silica gel 60 F_{254} precoated glass TLC plates, visualised using UV light and then basic potassium permanganate solution. Flash chromatography was performed using Merck silica gel (230–400 mesh) as the stationary phase. Melting points were determined using a Kopfler hot-stage apparatus and are uncorrected.

Infrared spectra were recorded using either a Perkin–Elmer FT 1600 or a Nicolet Avatar 360 FT-IR infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV400 or DRX500 spectrometer at ambient temperature. Chemical shifts are quoted relative to residual solvent and *J* values are given in hertz. Multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. Mass spectra were obtained on a Micromass Autospec or Micromass LCT instruments using electron impact (EI), fast atom bombardment (FAB) or electrospray (ES) ionisation. Specific rotations were measured using a Jasco DIP370 digital polarimeter at ambient conditions and are given in units of deg cm^2 g^{-1}; *c* is in g/100 mL of solvent. HPLC analysis was performed on a Hewlett–Packard 1100LC machine fitted with a diode array detector. All enantiomeric excesses were determined via HPLC comparison with racemates using Chiralcel OD-H or Chiralpak AD columns.

*4.1.1. (S)-tert-Butyl 2-(diphenylmethylene)amino-5-oxo-5-phenylpentanoate **13**.* Potassium hydroxide (19 mg, 0.34 mmol) was added to a solution of catalyst **6** (11 mg, 0.017 mmol) and mesitol (2.3 mg, 0.017 mmol) in dichloromethane (1 mL) at 0 °C under an atmosphere of argon and stirred at this temperature for 30 min. During this time a colour change from yellow to orange/brown was observed. The reaction was then cooled to −78 °C and a solution of the imine **5** (50 mg, 0.17 mmol) in dichloromethane (1 mL) added. PVK (34 mg, 0.26 mmol) in dichloromethane (1 mL) was then added dropwise over 2 h. The reaction mixture was stirred at −78 °C for a further 30 min, then filtered through a plug of $MgSO_4$, warmed to room temperature and concentrated under reduced pressure. The residue was generally used directly in the next step, but could also be purified by chromatography on silica gel to give the title compound **13** (72 mg, 99%, 89% ee) as a pale yellow oil. R_f 0.2 (10% EtOAc/petroleum ether); $[\alpha]_D^{23}$ −15.6 (*c* 0.70, $CHCl_3$, 89% ee); ν_{max} (film)/cm^{-1} 3006, 2976, 2933, 1731, 1685, 1150; δ_H (400 MHz, $CDCl_3$) 7.97–7.94 (2H, m, ArH), 7.67–7.64 (2H, m, ArH), 7.58–7.53 (1H, m, ArH), 7.48–7.30 (8H, m, ArH), 7.17–7.13 (2H, m, ArH), 4.08 (1H, dd, *J* 6.5, 5.5, H-2), 3.18–2.99 (2H, m, H_2-4), 2.36–2.22 (2H, m, H_2-3), 1.46 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 199.7 (C), 171.1 (C), 170.6 (C), 139.5 (C), 136.9 (C), 136.5 (C), 132.9 (CH), 130.3 (CH), 128.8 (CH), 128.6 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 81.2 (C), 64.8 (CH), 34.7 (CH_2), 28.2 (CH_2), 28.1 (CH_3); *m*/*z* (ESI$^+$) 428 (MH^+, 100%); HMRS (ESI$^+$) MH^+, found 428.2207. $C_{28}H_{30}NO_3^+$ requires 428.2220.

*4.1.2. (S)-2-tert-Butoxycarbonyl-5-phenyl-3,4-dihydro-2H-pyrrole **14** (general procedure for hydrolysis/cyclisation).* A solution of imine **13** (100 mg, 0.23 mmol) in 15% aqueous citric acid (1 mL) and tetrahydrofuran (2 mL) was stirred at room temperature for 2 h then diluted with dichloromethane (2 mL). The organic layer was washed with brine (3×3 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a yellow oil (52 mg). The product was purified by chromatography on silica gel to afford the title compound **14** (43 mg, 75%) as a colourless oil. R_f 0.2 (10% EtOAc/petroleum ether); $[\alpha]_D^{18}$ +88.0 (*c* 0.70, $CHCl_3$, 89% ee); ν_{max} (film)/cm^{-1} 2978, 1732, 1154; δ_H (400 MHz, $CDCl_3$) 7.90–7.88 (2H, m, ArH), 7.47–7.38 (3H, m, ArH), 4.84–4.80 (1H, m, H-2), 3.17–3.08 (1H, m, H_a-4), 3.02–2.95 (1H, m, H_b-4), 2.37–2.28 (1H, m, H_a-3), 2.21–2.12 (1H, m, H_b-3), 1.50 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 175.8 (C), 172.3 (C), 134.1 (C), 130.8 (CH), 128.5 (CH), 128.1 (CH), 81.1 (C), 75.4 (CH), 35.4 (CH_2), 28.1 (CH_3), 26.8 (CH_2); *m*/*z* (ESI$^+$) 246 (MH^+, 14%), 190 ($MH^+-C_4H_8$, 100); HMRS (ESI$^+$) MH^+, found 246.1487. $C_{15}H_{20}NO_2^+$ requires 246.1489. HPLC: column, Chiralcel OD-H;

mobile phase, hexane/isopropanol (90:10 v/v); flow rate 0.5 mL/min; retention times, 11.3 min (*S*), 19.8 min (*R*).

*4.1.3. (2S,5R)-tert-Butyl 5-phenylprolinate **15** (general procedure for hydrogenation).* A mixture of pyrroline **14** (590 mg, 2.4 mmol) and 5% Pt/C (Degussa F105 R/W, 58 mg) in methanol (10 mL) was stirred at room temperature under 15 psi of hydrogen for 3 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to afford a green-yellow oil (530 mg). The product was purified by chromatography on silica gel to afford the title compound **15** (520 mg, 2.1 mmol, 87%) as a colourless oil. R_f 0.15 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ +8.4 (*c* 0.70, $CHCl_3$, 89% ee); ν_{max} (film)/cm^{-1} 3354, 2975, 1726, 1154; δ_H (400 MHz, $CDCl_3$) 7.45 (2H, d, *J* 7.5, ArH), 7.34 (2H, dd, *J* 7.5, 7.5, ArH), 7.28–7.24 (1H, t, *J* 7.5, ArH), 4.18 (1H, dd, *J* 9.0, 6.0, H-2), 3.81 (1H, dd, *J* 8.5, 5.0, H-5), 2.25–1.64 (4H, m, H_2-3+H_2-4), 1.50 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 174.6 (C), 143.4 (C), 128.5 (CH), 127.1 (CH), 126.8 (CH), 81.1 (C), 63.8 (CH), 61.0 (CH), 34.3 (CH_2), 31.0 (CH_2), 28.1 (CH_3); *m*/*z* (ESI^+) 248 (MH^+, 18%), 192 ($MH^+C_4H_8$, 100); HMRS (ESI^+) MH^+, found 248.1639. $C_{15}H_{22}NO_2^+$ requires 248.1651. HPLC: column, Chiralcel AD; mobile phase, hexane/isopropanol (95:5 v/v); flow rate 0.75 mL/min; retention times, 11.0 min (*S*), 16.0 min (*R*).

*4.1.4. (+)-RP 66803, **11**.* HATU (230 mg, 0.60 mmol) was added to a solution of (3-*m*-tolylureido)acetic acid **16** (89 mg, 0.43 mmol) in anhydrous *N*,*N*-dimethylformamide (2 mL) at 0 °C. A solution of proline ester **15** (100 mg, 0.40 mmol) in *N*,*N*-dimethylformamide (2 mL) was then added, followed by *N*-methylmorpholine (0.19 mL, 0.60 mmol) and the resulting yellow solution stirred at 0 °C for 20 h. The reaction mixture was diluted with ethyl acetate (20 mL), washed with water (2×10 mL), 1 M hydrochloric acid (10 mL), saturated aqueous sodium hydrogen carbonate (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a yellow oil (200 mg). The crude product was crystallised from acetonitrile to afford the title compound **11** (130 mg, 0.30 mmol, 74%) as a colourless crystalline solid. Mp 153–155 °C (lit.[1] mp 156 °C); $[\alpha]_D^{23}$ +26.7 (*c* 1.1, MeOH, 89% ee) (lit.[1] $[\alpha]_D$ +36.0 (*c* 1.0, MeOH)); ν_{max} (film)/cm^{-1} 3356, 2978, 2931, 1736, 1637; δ_H (400 MHz, DMSO-d_6). At ambient temperature a 4:1 mixture of rotamers was observed, 8.66 (1H, s, CON*H*Ar), 7.65–7.03 (8H, m, ArH), 6.70 (0.2H, d, *J* 7.0, CON*H*Ar_{minor}), 6.68 (0.8H, d, *J* 7.0, ArH_{major}), 6.27 (0.2H, t *J* 5.5, CH_2NHCO_{minor}), 6.24 (0.8H, t, *J* 4.5, CH_2NHCO_{major}), 5.14 (0.8H, dd, *J* 8.0, 3.0, H-2_{major}), 4.70 (0.2H, dd, *J* 8.0, 4.0, H-2_{minor}), 5.01 (0.2H, t, *J* 7.0, H-5_{minor}), 4.31 (0.8H, t, *J* 7.5, H-5_{major}), 4.03 (0.2H, dd, *J* 170, 4.5, $COCH_aH_{bminor}$), 3.92 (0.8H, dd, *J* 14.5, 5.0, $COCH_aH_{bmajor}$), 3.84 (0.2H, dd, *J* 17.0, 5.5, $COCH_aH_{bminor}$), 3.20 (0.8H, dd, *J* 14.5, 4.5, $COCH_aH_{bmajor}$), 2.47–1.63 (4H, m, H_2-3+H_2-4), 2.23 (0.6H, s, $ArCH_{3minor}$), 2.21 (2.4H, s, $ArCH_{3major}$), 1.50 (1.8H, s, $C(CH_3)_{3minor}$), 1.47 (7.2H, s, $C(CH_3)_{3major}$); δ_C (100 MHz, DMSO-d_6) major rotamer 171.0 (C), 168.8 (C), 154.7 (C), 142.7 (C), 140.2 (C), 137.7 (C), 128.5 (CH), 128.4 (CH), 127.2 (CH), 126.1 (CH), 121.8 (CH), 118.0 (CH), 114.7 (CH), 80.7 (C), 61.4 (CH), 61.0 (CH), 42.0 (CH_2), 33.7 (CH_2), 26.8 (CH_2), 27.7 (CH_3), 21.2 (CH_3), minor rotamer 171.2 (C), 168.8 (C), 154.9 (C), 143.0 (C), 140.2 (C), 137.7 (C), 128.5 (CH), 127.9 (CH), 126.3 (CH), 125.9 (CH), 121.9 (CH), 118.1 (CH), 114.8 (CH), 81.9 (C), 62.5 (CH), 60.2 (CH), 41.8 (CH_2), 33.3 (CH_2), 29.6 (CH_2), 27.6 (CH_3), 21.2 (CH_3); *m*/*z* (ESI^+) 897 (M_2Na^+, 65%), 875 (M_2H^+, 28), 460 (MNa^+, 100), 438 (MH^+, 38); HMRS (ESI^+) MH^+, found 438.2384. $C_{25}H_{32}N_3O_4^+$ requires 438.2384. HPLC: Chiralcel AD; mobile phase, hexane/isopropanol (90:10 v/v); flow rate 0.75 mL/min; retention times, 20.0 min (2*R*,5*S*), 28.3 min (2*S*,5*R*). The above ^1H NMR spectrum is in agreement with that previously reported.[5]

4.2. General procedure for Michael additions

Potassium hydroxide (5.9 mmol) was added to a pre-cooled solution of catalyst **6** (0.3 mmol) and mesitol (0.3 mmol) in dichloromethane (5 mL) at 0 °C under an atmosphere of argon and stirred at this temperature for 45 min. During this period it is important that the reaction temperature does not exceed 0 °C. The mixture was then cooled to −78 °C and a pre-cooled solution of the imine **5** (3.0 mmol) in dichloromethane (4 mL) added dropwise. The mixture was stirred at −78 °C for 10 min, then a pre-cooled solution of the Michael acceptor (4.5 mmol) in dichloromethane (0.5 mL) was added dropwise. The resulting mixture was stirred at −78 °C until complete by TLC, then filtered through a plug of $MgSO_4$, warmed to room temperature and concentrated under reduced pressure to afford the crude product. Yields were determined by ^1H NMR using veratrole as an internal standard. For characterisation, an aliquot of the crude product was purified by chromatography on silica gel.

*4.2.1. (S)-tert-Butyl 2-(diphenylmethylene)amino-5-oxohexanoate, **17**.* Following the above general procedure, reaction of imine **5** (50 mg, 0.17 mmol) with MVK (72 μL, 0.85 mmol) for 2.5 h provided the title compound **17** (80%, 95% ee) as a colourless oil. R_f 0.7 (50% Et_2O/petroleum ether); $[\alpha]_D^{18}$ −76.9 (*c* 0.70, $CHCl_3$, 95% ee); ν_{max} ($CHCl_3$)/cm^{-1} 3083, 1717, 1601, 1369, 1153; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, m, ArH), 7.63 (1H, m, ArH), 7.46 (3H, m, ArH), 7.40–7.38 (2H, m, ArH), 7.37–7.33 (2H, m, ArH), 7.18–7.16 (1H, m, ArH), 3.97 (1H, dd, *J* 6.0, 6.0, H-2), 2.60–2.45 (2H, m, H_2-4), 2.22 (3H, s, H_3-6), 2.16–2.13 (2H, m, H_2-3), 1.44 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 208.5 (C), 171.0 (C), 170.6 (C), 139.5 (C), 136.5 (C), 130.4 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.1 (CH), 127.7 (CH), 81.2 (C), 64.7 (CH), 39.9 (CH_2), 29.9 (CH_3), 28.1 (CH_3), 27.7 (CH_2); *m*/*z* (ESI^+) 388 (MNa^+, 13%), 366 (MH^+, 100), 310 ($MH^+C_4H_8$, 51); HMRS (ESI^+) MH^+, found 366.2062. $C_{19}H_{28}NO_3^+$ requires 366.2068. HPLC: Chiralcel OD-H; mobile phase, hexane/ethanol (99:1 v/v); flow rate, 0.5 mL/min; retention times, 15.2 min (*R*), 17.7 min (*S*). The ^1H NMR spectrum is in agreement with that previously reported.[24]

*4.2.2. (S)-tert-Butyl 2-(diphenylmethylene)amino-5-oxononanoate, **18**.* Following the above general procedure, reaction of imine **5** (878 mg, 2.97 mmol) with hept-1-en-3-one (500 mg, 4.46 mmol) for 8 h provided the title compound **18** (100%, 96% ee) as a yellow oil. R_f 0.45 (10% EtOAc/petroleum ether); $[\alpha]_D^{21}$ −53.4 (*c* 0.70, $CHCl_3$, 96% ee); ν_{max} ($CHCl_3$)/cm^{-1} 3006, 2962, 2934, 2874, 1726, 1153; δ_H (400 MHz, $CDCl_3$) 7.63 (2H, d, *J* 9.0, ArH), 7.48–7.42 (3H, m, ArH), 7.36–7.31 (3H, m, ArH), 7.18–7.15 (2H, m, ArH), 3.95 (1H, dd, *J* 6.0, 6.0, H-2), 2.59–2.47 (2H, m, H_2-4), 2.41 (2H, t, *J* 7.5, H_2-6), 2.21–2.15 (2H, m, H_2-3), 1.58–1.50 (2H, m, H_2-7), 1.44 (9H, s, $C(CH_3)_3$), 1.35–1.25 (2H, m, H_2-8), 0.88 (3H, t, *J* 7.0, H_3-9); δ_C (100 MHz, $CDCl_3$) 210.7 (C), 171.1 (C), 170.4 (C), 139.5 (C), 136.5 (C), 130.3 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 127.7 (CH), 81.1 (C), 64.8 (CH), 42.6 (CH_2), 38.9 (CH_2), 28.1 (CH_3), 27.8 (CH_2), 25.9 (CH_2), 22.4 (CH_2), 13.9 (CH_3); *m*/*z* (ESI^+) 408 (MH^+, 100%); HMRS (ESI^+) MH^+, found 408.2518. $C_{26}H_{34}NO_3^+$ requires 408.2460. HPLC: Chiralcel OD-H; mobile phase, hexane/isopropanol (99:1 v/v); flow rate, 0.9 mL/min; retention times, 9.3 min (*R*), 12.3 min (*S*).

*4.2.3. (S)-2-tert-Butoxycarbonyl-5-methyl-3,4-dihydro-2H-pyrrole, **19**.* Crude imine **17** (1.2 g, 3.4 mmol) was reacted with 15% aqueous citric acid following the above procedure to afford the title compound **19** (550 mg, 3.0 mmol, 88%) as a yellow oil. R_f 0.3 (20% EtOAc/petroleum ether); $[\alpha]_D^{21}$ +81.8 (*c* 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 2957, 1732, 1648, 1368, 1156; δ_H (400 MHz, $CDCl_3$) 4.57–4.52 (1H, m, H-2), 2.64–2.49 (2H, m, H_2-4), 2.20–1.97 (2H, m, H_2-3), 2.09 (3H, s, CH_3), 1.48 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 178.2 (C), 172.6 (C), 81.0 (C), 75.0 (CH), 39.2 (CH_2), 28.1 (CH_3), 26.9 (CH_2), 19.8 (CH_3); *m*/*z* (ESI^+) 367 (M_2H^+, 42%), 184 (MH^+, 100); HMRS (ESI^+) MH^+, found 184.1329. $C_{10}H_{18}NO_2^+$ requires 184.1332.

*4.2.4. (S)-tert-Butyl 2-butyl-1-pyrroline-5-carboxylate, **20**.* Crude imine **18** (2.97 mmol) was reacted with 15% aqueous citric acid

following the above procedure to afford the title compound **20** (594 mg, 89%, 96% ee) as a colourless oil. R_f 0.25 (50% Et_2O/petroleum ether); $[\alpha]_D^{22}$ +96.6 (*c* 0.78, EtOH, 96% ee), [lit.[3] $[\alpha]_D$+90.8 (*c* 5.1, EtOH)]; δ_H (400 MHz, $CDCl_3$) 4.60–4.56 (1H, m, H-2), 2.65 (1H, dddd, *J* 17.5, 10.0, 6.0, 1.5, H_a-4), 2.50 (1H, dddd, *J* 17.5, 10.0, 6.0, 1.5, H_b-4), 2.41 (2H, dt, *J* 8.0, 1.5, 2H-6), 2.15 (1H, dddd, *J* 13.0, 10.0, 9.0, 6.0, H_a-3), 1.99 (1H, dddd, *J* 13.0, 10.0, 6.0, 6.0, H_b-3), 1.65–1.58 (2H, m, 2H-7), 1.49 (9H, s, $C(CH_3)_3$), 1.45–1.33 (2H, m, 2H-8), 0.92 (3H, t, *J* 7.5, CH_3); δ_C (100 MHz, $CDCl_3$) 181.8 (C), 172.7 (C), 80.9 (C), 74.8 (CH), 37.5 (CH_2), 33.5 (CH_2), 28.6 (CH_2), 28.0 (CH_3), 26.7 (CH_2), 22.5 (CH_2), 13.9 (CH_3); *m*/*z* (ESI^+) 473 (M_2Na^+, 53%), 451 (M_2H^+, 87%), 226 (MH^+, 100%); HMRS (ESI^+) MH^+, found 226.1808. $C_{13}H_{24}NO_2^+$ requires 226.1802. HPLC: Chiracel OD-H; mobile phase, hexane/isopropanol (99:1 v/v); flow rate 0.7 mL/min; retention times, 10.5 min (*S*), 16.8 min (*R*). The ^1H NMR spectrum is in agreement with that previously reported.[22b]

4.2.5. (2S,5S)-tert-Butyl 5-methylprolinate, ***21****.* Pyrroline **19** (550 mg, 3.0 mmol) was hydrogenated for 3 h following the procedure described above to afford the title compound **21** (100%) as a yellow oil. R_f 0.1 (50% Et_2O/petroleum ether); $[\alpha]_D^{24}$ −15.8 (*c* 0.70, $CHCl_3$, 95% ee), [lit.[4] $[\alpha]_D$ −11.8 (*c* 0.74, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 3.62 (1H, dd, *J* 9.0, 5.5, H-2), 3.16–3.10 (1H, m, H-5), 2.11–2.05 (1H, m, H_a-3), 1.91–1.83 (2H, m, H_b-3+H_a-4), 1.47 (9H, s, $C(CH_3)_3$), 1.27–1.11 (1H, m, H_b-4), 1.22 (3H, d, *J* 6.5, CH_3). The ^1H NMR spectrum is in agreement with that previously reported.[21]

4.2.6. (2S, 5S)-tert-Butyl 5-butyl-pyrrolidine-2-carboxylate ***22****.* Pyrroline **20** (500 mg, 2.22 mmol) was hydrogenated for 6 h following the procedure described above to afford the title compound **22** (87%, 96% ee) a colourless oil. R_f 0.1 (50% Et_2O/petroleum ether); $[\alpha]_D^{24}$ −25.6 (*c* 0.34, EtOH, 96% ee), [lit.[5] $[\alpha]_D$ −18.8 (*c* 0.8, EtOH)]; δ_H (100 MHz, $CDCl_3$) 3.63 (1H, dd, *J* 9.0, 5.5, H-2), 3.04–2.97 (1H, m, H-5), 2.12–2.02 (1H, m, H_a-3), 1.91–1.83 (3H, m, H_b-3, H_a-4, NH), 1.63–1.55 (1H, m, H_a-6), 1.51–1.45 (1H, m, H_b-6), 1.48 (9H, s, $C(CH_3)_3$), 1.44–1.32 (4H, m, 2H-8, 2H-7), 1.27–1.17 (1H, m, H_b-4), 0.92 (3H, br t, *J* 7.0, CH_3); δ_C (75 MHz, $CDCl_3$) 174.7 (C), 80.9 (C), 60.7 (CH), 60.4 (CH), 35.6 (CH_2), 31.9 (CH_2), 30.8 (CH_2), 29.6 (CH_2), 28.1 (CH_3), 22.8 (CH_2), 14.1 (CH_3); *m*/*z* (ESI^+) 455 (M_2H^+, 83%), 228 (MH^+, 100%), 173 ($MH^+C_4H_8$, 11%); HMRS (ESI^+) MH^+, found 228.1974. $C_{13}H_{26}NO_2^+$ requires 228.1958. HPLC: column, Chiracel AD-H; mobile phase, hexane/ethanol (97:3 v/v); flow rate 0.8 mL/min; retention times, 18.8 min (*S*), 22.4 min (*R*). The ^1H NMR spectrum is in agreement with that previously reported.[17]

Acknowledgements

Financial support for this work was provided by EPSRC and GSK.

References and notes

1. CrossFire Beilstein Database: Copyright© 2007, Elsevier Information Systems GmbH.
2. Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139–165; Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556–1575.
3. Wink, M. In *Modern Alkaloids*; Fattorusso, E., Taglialatela-Scafati, O., Eds.; Wiley-VCH: Weinheim, 2008; pp 3–23; Aniszewski, T. *Alkaloids—Secrets of Life*; Elsevier: Amsterdam, 2007; Roberts, M. F.; Wink, M. *Alkaloids, Biochemistry, Ecology and Medicinal Applications*; Plenum: New York, NY, 1998.
4. Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854.
5. Manfre, F.; Pulicani, J. P. *Tetrahedron: Asymmetry* **1994**, *5*, 235–238 Rhone-Poulenc Rorer, 1993 WO 9301167-A.
6. Pei, Z.; Li, X.; Longenecker, K.; von Geldern, T. W.; Wiedeman, P. E.; Lubben, T. H.; Zinker, B. A.; Stewart, K.; Ballaron, S. J.; Stashko, M. A.; Mika, A. K.; Beno, D. W. A.; Long, M.; Wells, H.; Kempf-Grote, A. J.; Madar, D. J.; McDermott, T. S.; Bhagavatula, L.; Fickes, M. G.; Pireh, D.; Solomon, L. R.; Lake, M. R.; Edalji, R.; Fry, E. H.; Sham, H. L.; Trevillyan, J. M. *J. Med. Chem.* **2006**, *49*, 3520–3535; Fournie-Zaluski, M.-C.; Coric, P.; Thery, V.; Gonzales, W.; Meudal, H.; Turcaud, S.; Michel, J.-B.; Roques, B. P. *J. Med. Chem.* **1996**, *39*, 2594–2608.
7. Davies, H. M. L.; Panaro, S. A. *Tetrahedron Lett.* **1999**, *40*, 5287–5290.
8. Panday, S. K.; Prasad, J.; Dikshit, D. K. *Tetrahedron: Asymmetry* **2009**, *20*, 1581–1632; Najera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245–2303.
9. For lead references see: (a) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409–1412; (b) Llamas, T.; Gomez-Arrayas, R. G.; Carretero, J. C. *Org. Lett.* **2006**, *8*, 1795–1798; (c) van Esseveldt, B. C. J.; Vervoort, P. W. H.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 1791–1795.
10. Lygo, B.; Beaumont, D. J. *Chimia* **2007**, *61*, 257–262; Lygo, B.; Andrews, B. I.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **2002**, *43*, 8015–8018; Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289–6300.
11. Lygo, B.; Beynon, C.; Lumley, C.; McLeod, M. C.; Wade, C. E. *Tetrahedron Lett.* **2009**, *50*, 3363–3365.
12. For a closely related sequence involving analogous bis-*tert*-butylmethyl esters see Wang, Y.-G.; Kumano, T.; Kano, T.; Maruoka, K. *Org. Lett.* **2009**, *11*, 2027–2029.
13. van der Werf, A.; Kellogg, R. M. *Tetrahedron Lett.* **1991**, *32*, 3727–3730.
14. Black, D. S.; Edwards, G. L.; Evans, R. H.; Keller, P. A.; Laaman, S. M. *Tetrahedron* **2000**, *56*, 1889–1898.
15. For previous synthetic approaches to this target see Refs. 5,9a,c,14 and Rudolph, A. C.; Machauer, R.; Martin, S,F. *Tetrahedron Lett.* **2004**, *45*, 4895–4898; Severino, E. A.; Costenaro, E. R.; Garcia, A. L. L.; Correia, C. R. D. *Org. Lett.* **2003**, *5*, 305–308; Davis, F. A.; Fang, T.; Goswami, R. *Org. Lett.* **2002**, *4*, 1599–1602; Haddad, M.; Imogai, H.; Larcheveque, M. *J. Org. Chem.* **1998**, *63*, 5680–5683.
16. Enantiomeric excesses were determined via HPLC comparison with racemates using Chiralcel OD-H or Chiralpak AD columns.
17. Ibrahim, H. H.; Lubell, W. D. *J. Org. Chem.* **1993**, *58*, 6438–6441.
18. F105 R/W 5% Pt/C (Degussa) and JM 117 5% Pt/C (Johnson Matthey) gave similar rates of reaction.
19. Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539–4547.
20. Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518–525.
21. Mota, A. J.; Chiaroni, A.; Langlois, N. *Eur. J. Org. Chem.* **2003**, 4187–4198.
22. (a) Wistrand, L.-G.; Skrinjar, M. *Tetrahedron* **1991**, *47*, 573–582; (b) Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229–1239.
23. See for example: Toyooka, N.; Zhou, D.; Nemoto, H.; Tezuka, Y.; Kadota, S.; Jones, T. H.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Synlett* **2008**, 1894–1896.
24. O'Donnell, M. J.; Delgardo, F.; Dominguez, E.; de Blas, J.; Scott, W. L. *Tetrahedron: Asymmetry* **2001**, *12*, 821–828.