The synthesis of Enantiomerically Pure 2,2,3,4,5-Pentasubstituted Pyrrolidines by Phenylsulfanyl Migration

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Supporting Information

General Information

All reactions were carried out using freshly distilled solvents. NMR spectra were carried out on Bruker 400 and 500 MHz spectrometers and assignments are based on ^{1}H (coupling constants are rounded to the nearest 0.5Hz), ^{13}C, COSY, DEPT-135 and HMQC spectra. Optical rotations were recorded on a Perkin Elmer 241 polarimeter using the sodium D line at room temperature and are given in units of 10^{-1} deg dm^2 g^{-1}, with concentrations quoted in units of g / 100 mL. Infra-red spectra were recorded using a Perkin Elmer 1600 (FT-IR) spectrometer.

Experimental

(3*R*, 4*R*, 5*S*, 1'*S*) Ethyl 5-[*N*-allyl-*N*-(1'-phenylethyl)amino]-3-hydroxyl-2-methyl-2-phenylsulfanyl-hexane-4-carboxylate (12)

The ester **10** (2.5 g, 9.1 mmol) as added to a solution of LDA (0.010 mol) in THF (200 mL), followed after 30 mins by $B(OMe)_3$ (1.9 g, 2.2 mL, 0.018 mol). After a further 30 mins the aldehyde **15** (4.1 g, 0.023 mol) was added. After 4-5 h the reaction was quenched with $NH_4Cl_{sat.aq.}$ and concentrated. The residue was dissolved in EtOAc and washed with water and brine, dried over Na_2SO_4 and concentrated. ^{1}H-NMR spectroscopy of the crude product indicated a c.a. 6:1 mixture of diastereoisomers. Column chromatography, eluting a gradient of 1-5% ether / 30-40 pet. ether, produced the *β-hydroxy ester* **12** as a clear colourless oil (2.9 g, 6.3 mmol, 69%) as a ~10:1 mixture of diastereoisomers;

δ_H (400 MHz, $CDCl_3$) 1.10 (s, 3H, PhSC***Me***Me), 1.22 (t, *J* 7.0Hz, 3H, CO_2CH_2***Me***), 1.23 (s, 3H, PhSCMe***Me***), 1.42 (d, *J* 7.0Hz, 6H, PhCH***Me*** + ***Me***CH), 3.20-3.35 (m, 3H, NC***H*****$_2$**CH + C***H***CO_2), 3.44 (qd, *J* 7.0Hz, 4.0Hz, 1H, MeC***H***CH), 4.08 (q, *J* 7.0Hz, 2H, CO_2C***H*****$_2$**), 4.21 (dd, *J* 9.5Hz, 1.0Hz, 1H, HOC***H***), 4.41 (q, *J* 7.0Hz, 1H, PhC***H***), 4.98 (dd, *J* 10.0Hz, 1.5Hz, 1H, CH=CH_2, *cis*), 5.02 (dd, *J* 17.0Hz, 1.5Hz, 1H, CH=CH_2, *trans*), 5.78 (ddt, *J* 17.0Hz, 10.0Hz, 6.5Hz, 1H, CH_2C***H***CH_2), 6.61 (br s, 1H, ***H***OCH), 7.25-7.37 (m, 8H, Ph), 7.56 (dd, *J* 8.0Hz, 1.5Hz, 2H, Ph);

δ_C (100 MHz, $CDCl_3$) 14.0 (CO_2CH_2***Me***), 14.4 (PhCH***Me***), 15.8 (***Me***CH), 25.0 (PhSC***Me***Me), 26.0 (PhSCMe***Me***), 47.2 (C***H***CO_2), 49.7 (N***C***H_2CH), 55.1 (PhS***C***Me_2), 57.0 (Me***C***H), 57.3 (Ph***C***H), 60.6 (CO_2***C***H_2), 76.1 (HO***C***H), 116.4 (NCH_2CH***C***H_2), 127.1 (*p*-***C***H), 128.2 (*m*-***C***H), 128.3 (*m*-***C***H), 128.4 (*o*-***C***H), 128.6 (*p*-***C***H, PhS), 131.8 (*i*-***C***), 137.7 (*o*-***C***H), 137.7 (NCH_2***C***H), 142.0 (*i*-***C***), 173.2 (***C***O_2);

IR (cm^{-1}, CH_2Cl_2) *v*: 1728 (C=O);

LRMS (ESI+): *m/z* 456 (35%, M+1);

HRMS (ESI+): *m/z* 456.25655 ($C_{27}H_{38}NO_3S$, MH requires *M* 456.25724);

Anal. Calcd for $C_{27}H_{37}NO_3S$ C 71.17, H 8.10, N 3.07; Found C 71.11, H 8.14, N 3.04.

(3*R*, 4*S*, 5*S*, 1'*S*) Ethyl 5-[*N*-benzyl-*N*-(1'-phenylethyl)amino]-3-hydroxyl-2-methyl-2-phenylsulfanyl-hexane-4-carboxylate (14)

(α–Methylbenzyl)benzylamine (13.0 g, 0.062 mol) and ^{n}BuLi (27 mL, 2.3 M, 0.062 mol) were combined in THF (600 mL) at –78°C. After 30 mins ethyl crotonate (6.4 g, 7.0 mL, 0.056 mol) was added followed after 1 h by the aldehyde **15** (25.0 g, 0.14 mol). After a further 3-4h the reaction was quenched with $NH_4Cl_{sat.aq.}$ and concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with water and brine and dried over Na_2SO_4. The resulting oil was purified by column chromatography eluting a gradient of 5-15% ether / 30-40 pet. ether to give the *β-hydroxy ester* **14** as a clear colourless oil (19.8 g, 0.039 mol, 70%, ~4:1d.r.). The diastereomeric ratio of the crude reaction product could not be obtained from its ^{1}H-NMR spectrum;

δ_H (400 MHz, $CDCl_3$) 1.03 (s, 3H, PhSC***Me***Me), 1.05 (s, 3H, PhSCMe***Me***), 1.08 (d, *J* 7.0Hz, 3H, ***Me***CHCH), 1.25 (t, *J* 7.0.Hz, 3H, CO_2CH_2***Me***), 1.41 (d, *J* 7.0Hz, 3H, PhCH***Me***), 2.59 (dd, *J* 9.5Hz, 1.5Hz, 1H, C***H***CO_2), 3.40 (d, *J* 8.5Hz, 1H, O***H***), 3.51 (dq, *J* 9.5Hz, 7.5Hz, 1H, MeC***H***CH), 3.70 (d, *J* 14.0Hz, 1H, PhC***H***$_A$$H_B$N), 3.75 (d, *J* 14.0Hz, 1H, PhCH_A***H***$_B$N), 3.84 (dd, *J* 8.5Hz, 1.5Hz, 1H, HOC***H***), 4.05 (q, *J* 7.0Hz, 1H, PhC***H***Me), 4.08 (dq, *J* 11.0Hz, 7.0Hz, 1H, CO_2C***H***$_A$$H_B$), 4.13 (dq, *J* 11.0Hz, 7.0Hz, 1H, CO_2CH_A***H***$_B$), 7.20-7.56 (m, 15H, Ph);

δ_C (100 MHz, $CDCl_3$) 13.9 (CO_2CH_2***Me***), 15.0 (***Me***CH), 16.5 (PhCH***Me***), 25.0 (PhSC***Me***Me), 26.0 (PhSCMe***Me***), 49.3 (N***C***H_2Ph), 49.8 (**C**HCO_2), 53.5 (Me***C***HCH), 54.4 (PhS***C***$(CH_3)_2$), 58.9 (Ph***C***HCH_3), 60.7 (CO_2***C***H_2), 75.5 (HO***C***H), 126.7 (*p*-***C***H), 126.8 (*p*-***C***H), 128.0, 128.1, 128.2, 128.4 (Ar), 128.7 (*p*-***C***H, PhS), 128.9 (Ar), 131.9 (*i*-***C***), 137.8 (*o*-***C***H, PhS), 140.9 (*i*-***C***), 143.8 (*i*-***C***), 175.4 (***C***O);

IR (cm^{-1}, CH_2Cl_2) *v*: 1731 (C=O);

LRMS (EI+): *m/z* 396.3 (35%, M-SPh);

HRMS (EI+): *m/z* 396.25387 ($C_{25}H_{34}NO_3$, M-SPh requires *M* 396.25332);

Anal. Calcd for $C_{31}H_{39}NO_3S$ C 73.63, H 7.77, N 2.77; Found C 73.58, H 7.82, N 2.94.

(3*R*, 4*R*, 5*S*, 1'*S*) Ethyl 5-[*N*-(1'-phenylethyl)amino]-3-hydroxyl-2-methyl-2-phenylsulfanyl-hexane-4-carboxylate (17)

The amine **12** (1.0 g, 2.2 mmol), DPPB (187 mg, 0.44 mmol), *o*-mercaptobenzoic acid (500 mg, 3.29 mmol) and allyl palladium chloride dimer (40 mg, 0.11 mmol) were dissolved in THF (30 mL). The reaction mixture was left to stir overnight. The reaction mixture was concentrated under reduced pressure and the residue dissolved in EtOAc and washed with $NaHCO_3$ (×3), water and brine before being dried over Na_2SO_4 and concentrated. The resulting red oil was purified by column chromatography eluting isochromatically with 15:1 hexane:EtOAc to give the *amine* **17** as a clear colourless oil (800 mg, 1.9 mmol, 88% yield, >13:1 d.r.);

δ_H (400 MHz, $CDCl_3$) 1.19 (s, 3H, PhSC***Me***Me), 1.20 (t, *J* 7.0Hz, 3H, CO_2CH_2***Me***), 1.21 (d, *J* 6.5Hz, 3H, ***Me***CH), 1.32 (s, 3H, PhSCMe***Me***), 1.38 (d, *J* 6.5Hz, 3H, PhCH***Me***), 3.17 (dd, *J* 7.0Hz, 3.5Hz, 1H, C***H***CO_2), 3.28 (qd, *J* 6.5Hz, 3.5Hz, 1H, MeC***H***), 4.01 (q, *J* 6.5Hz, 1H, PhC***H***), 4.08 (q, *J* 7.0Hz, 2H, CO_2C***H*****$_2$**), 4.17 (d, *J* 7.0Hz, 1H, HOC***H***), 7.25-7.40 (m, 8H, Ph), 7.61 (dd, *J* 5.5Hz, 1.5Hz, 2H, Ph);

δ_C (125 MHz, $CDCl_3$) 13.9 (***Me***), 17.3 (***Me***), 22.7 (***Me***), 25.6 (***Me***), 25.7 (***Me***), 47.8 (***C***H), 51.2 (***C***H), 54.3 (***C***H), 54.7 (PhS***C***), 60.6 (***C***H_2), 77.7 (***C***H), 126.4 (*m*-***C***H), 127.3 (*p*-***C***H), 128.4 (*m*-***C***H), 128.6 (*p*-***C***H, PhS), 128.6 (*o*-***C***H), 131.7 (*i*-***C***), 137.7 (*o*-***C***H, PhS), 144.9 (*i*-***C***), 173.58 (***C***O);

IR (cm^{-1}, CH_2Cl_2) *v*: 3684 (w, NH), 3051 (b, OH), 2976 (CH), 1714 (C=O);

LRMS (ESI+): *m/z* 416 (64%, M+1);

HRSM (ESI+): *m/z* 416.22265 ($C_{24}H_{34}NO_3S$, MH requires *M* 416.22594);

Anal. Calcd for $C_{24}H_{33}NO_3S$ C 69.36, H 8.00, N 3.37; Found C 69.27, H 8.02, N 3.46.

(3*R*, 4*S*, 5*S*, 1'*S*) Ethyl 5-[*N*-(1'-phenylethyl)amino]-3-hydroxyl-2-methyl-2-phenylsulfanyl-hexane-4-carboxylate (18)

The alcohol **14** (0.5 g, 0.99 mmol) and ceric ammonium nitrate (1.14 g, 2.1 mmol) were dissolved in MeCN / H_2O (5:1, 10 mL) left to stir overnight. The reaction mixture quenched with $NaHCO_3$ and EtOAc. The organic layer was removed and washed with $NaHCO_3$ (×3) water and brine before being dried over Na_2SO_4 and concentrated. The *amino alcohol* **18**, a clear colourless oil, a 4-5:1 mixture of diastereoisomers (290 mg, 0.7 mmol, 71%) was isolated by chromatography eluting isochromatically 8:1 hexane:EtOAc;

δ_H (500 MHz, $CDCl_3$) 1.07 (d, *J* 6.5Hz, 3H, ***Me***CH), 1.20 (s, 3H, ***Me***MeC), 1.25 (s, 3H, Me***Me***C), 1.31 (d, *J* 6.5Hz, 3H, PhCH***Me***), 1.33 (t, *J* 7.0 Hz, CO_2CH_2***Me***), 3.05 (quintet, *J* 6.5Hz, 1H, MeC***H***), 3.21 (dd, *J* 7.0 Hz, 1.0Hz, 1H, C***H***CO_2), 3.81 (d, *J* 1.0Hz, 1H, HOC***H***), 4.03 (q, *J* 6.5Hz, 1H, PhC***H***), 4.18 (dq, *J* 11.0Hz, 7.0Hz, 1H, CO_2C***H***H), 4.24 (dq, *J* 11.0, 7.0Hz, 1H, CO_2CH***H***), 7.28 (m, 2H, *p*-CPh + Ph), 7.32-7.41 (m, 6H, Ph), 7.45 (dd, *J* 8.0Hz, 1.5Hz, 2H, *o*-Ph);

δ_C (125 MHz, $CDCl_3$) 14.1 (CO_2CH_2***Me***), 19.6 (***Me***CH), 23.9 (***Me***MeC), 24.3 (Me***Me***C), 26.2 (PhCH***Me***), 48.4 (***C***HCO_2), 52.6 (Me***C***H), 53.7 (MeMe***C***), 55.6 (Ph***C***H), 60.8 (CO_2***C***H_2), 75.8 (HO***C***H), 126.6 (*m*-***C***H), 126.9 (*p*-***C***H), 128.5 (*o*-***C***H), 128.5 (*m*-**C**H, PhS), 128.8 (*p*-***C***H, PhS), 131.3 (*i*-***C***), 137.7 (*o*-***C***H, PhS), 146.1 (*i*-***C***), 175.6 (***C***O);

IR (cm^{-1}, CH_2Cl_2) *v*: 3900 (NH), 1701 (C=O);

LRMS (EI+): *m/z* 306.2 (53%, M-SPh);

HRMS (EI+): *m/z* 306.20619 ($C_{18}H_{28}NO_3$, M-SPh requires *M* 306.20637);

Anal. Calcd for $C_{24}H_{33}NO_3S$ C 69.36, N 8.00, N 3.37; Found C 68.96, H 7.93, N 3.49.

(3*S*, 4*S*, 5*S*, 1'*S*)-Ethyl-2,2,5-trimethyl-1-(1'-phenylethyl)-3-phenylsulfanyl-pyrrolidin-4-carboxylate (19)

The amine **17** (700 mg, 1.6 mmol), CDI (300 mg, 1.8 mmol) and DMAP (24 mg, 0.16 mmol) were dissolved in MeCN (16 mL) and heated at reflux overnight. The reaction mixture was concentrated onto silica and chromatographed eluting 5% EtOAc in hexane to give the *pyrrolidine* **19** as a clear colourless oil (601 mg, 1.5 mmol, 90%, >20:1 d.r.);

δ_H (400 MHz, $CDCl_3$) 0.84 (d, *J* 6.0Hz, 3H, ***Me***CH), 1.13 (t, *J* 7.0Hz, 3H, CO_2CH_2**C*H*$_3$**), 1.15 (s, 3H, PhSC***Me***Me), 1.19 (s, 3H, PhSCMe***Me***), 1.45 (d, *J* 7.0Hz, 3H, PhCH***Me***), 2.99 (dd, *J* 12.0Hz,

10.0Hz, 1H, C***H***CO_2), 3.09 (dq, *J* 10.0Hz, 6.0Hz, 1H, MeC***H***), 3.69 (d, *J* 12.0Hz, 1H, PhSC***H***), 3.98 (dq, *J* 11.0Hz, 7.0Hz, 1H, $CO_2C\boldsymbol{H_A}H_B$), 4.03 (dq, *J* 11.0Hz, 7.0Hz, 1H, $CO_2CH_A\boldsymbol{H_B}$), 4.16 (q, *J* 7.0Hz, 1H, PhC***H***), 7.20-7.35 (m, 8H, Ph), 7.55 (dd, *J* 8.0Hz, 1.5Hz, 2H, Ph);

δ_C (125 MHz, $CDCl_3$) 14.1 ($CO_2CH_2\boldsymbol{Me}$), 20.2 (***Me***CH), 20.4 (PhSC***Me***Me), 23.6 (PhCH***Me***), 28.1 (PhSCMe***Me***), 52.4 (***C***HCO_2), 52.5 (Me***C***H), 53.6 (Ph***C***H), 59.8 (PhS***C***H), 60.4 ($CO_2\boldsymbol{C}H_2$), 64.5 (N***C***Me_2), 126.6 (*p*-***C***H), 127.0 (*p*-***C***H, PhS), 127.9 (*m*-***C***H), 128.5 (*o*-***C***H), 128.7 (*m*-***C***H), 132.3 (*o*-***C***H, PhS), 136.0 (*i*-***C***), 142.3 (*i*-***C***, PhS), 171.8 (***C***O_2);

IR (cm^{-1}, CH_2Cl_2) *v*: 1730 (C=O);

LRMS (ESI+): *m/z* 420.2 (93, M+Na), 398.2 (100, M+1);

HRMS (ESI+): *m/z* 398.21450 ($C_{24}H_{32}NO_2S$, MH requires *M* 398.21537);

Anal. Calcd for $C_{24}H_{31}NO_2S$ C 72.50, H 7.86, N 3.52; Found C 72.57, H 7.90, N 3.77.

$[\alpha]_D^{20}$ +9.83 (c = 1.475, $CHCl_3$)

(3*S*, 4*R*, 5*S*, 1'*S*)-Ethyl-2,2,5-trimethyl-1-(1'-phenylethyl)-3-phenylsulfanyl-pyrrolidin-4-carboxylate (20)

The amine **18** (100 mg, 0.24 mmol, ~4:1 d.r.), CDI (43 mg, 0.27 mmol) and DMAP (cat.) were heated at reflux in MeCN (3 mL) overnight. The reaction mixture was concentrated onto silica and chromatographed eluting 12:1 hexane:EtOAc to give the *pyrrolidine* **20,** a clear colourless oil, as a single diastereoisomer (40 mg, 0.10 mmol, 42%);

δ_H (400 MHz, $CDCl_3$) 1.02 (d, *J* 6.0Hz, 3H, ***Me***CH), 1.11 (t, *J* 7.0Hz, 3H, $CO_3CH_2C\boldsymbol{H_3}$), 1.25 (s, 3H, NC***Me***), 1.31 (s, 3H, NC***Me***), 1.51 (d, *J* 7.0Hz, 3H, PhCH***Me***), 2.97 (dd, *J* 10.0Hz, 6.0Hz, 1H, C***H***CO_2), 3.38 (qn, *J* 6.0Hz, 1H, $CH_3C\boldsymbol{H}$), 3.51 (d, *J* 10.0Hz, 1H, PhSC***H***), 4.07 (q, *J* 7.0Hz, 2H, $CO_2C\boldsymbol{H_2}$), 4.24 (q, *J* 7.0Hz, 1H, PhC***H***Me), 7.20-7.45 (m, 10H, aromatics);

δ_C (100 MHz, $CDCl_3$) 15.3 ($CO_2CH_2\boldsymbol{Me}$), 21.4 (NC***Me***), 23.8 (PhCH***Me***), 24.9 (***Me***CH), 30.8 (NC***Me***), 54.1 (Ph***C***HMe), 57.3 (***C***HCO_2), 57.4 (Me***C***H), 60.7 (PhS***C***H), 61.8 ($CO_2\boldsymbol{C}H_2Me$), 67.0 (***C***Me_2), 127.5 (*p*-***C***H), 127.8 (*p*-***C***H), 129.1, 129.9, 130.1, 131.5 (Ar), 138.8 (*i*-***C***), 143.9 (*i*-***C***), 174.2 (***C***O_2);

IR (cm^{-1} in CH_2Cl_2) *v*: 1728 (C=O);

LRMS (ESI+): *m/z* 420.2 (80%, M+Na), 398.2 (100, M+1);

HRMS (ESI+): *m/z* 398.21550 ($C_{24}H_{32}NO_2S$, MH requires *M* 398.21537);

Anal. Calcd for $C_{24}H_{31}NO_2S$ C 72.50, H 7.86, N 3.52; Found C 72.40, H 7.78, N 3.49.

$[\alpha]_D^{23}$ +98.3 (c = 1.00, $CHCl_3$)

After removal of the benzyl groups over $Pd(OH_2)$, the enantiomeric excesses of both pyrrolidines could be measured. The resulting amines were reacted with both enantiomers of the acid chloride derived from Mosher's acid. Comparison of the 400 MHz ^{1}H-NMR spectra of these compounds indicated that both pyrrolidines had >95% e.e.