Evaluating β-amino acids as enantioselective organocatalysts of the Hajos-Parrish-Eder-Sauer-Wiechert Reaction

Stephen G. Davies,* Angela J. Russell, Ruth L. Sheppard, Andrew D. Smith and James E. Thomson

Department of Organic Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK.

e-mail: steve.davies@chem.ox.ac.uk

Experimental

General Experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[1] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (thin film) or a KBr disc (KBr disc), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF and were internally calibrated with polyanaline in positive and

[1] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, *Organometallics*, 1996, **15**, 1518.

negative modes, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

General Procedure 1: Triketone preparation

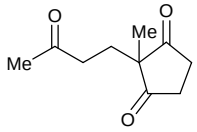
Et_3N (1.5 eq) was added to a stirred solution of the 1,3-diketone (1.0 eq) in EtOAc at rt. The resultant solution was allowed to stir for 30 min before addition of the requisite vinyl ketone (1.5 eq). The reaction mixture was then left stirring for 5 days after which time volatiles were removed *in vacuo*. The residue was then re-dissolved in DCM and the resultant solution was filtered and concentrated *in vacuo*.

General Procedure 2: Hajos-Parrish-Eder-Sauer-Weichert reaction

Part A: A catalyst (30 mol %) was added to a stirred solution of triketone (1.0 eq) in anhydrous DMF at either rt or 60 ºC. After the designated reaction time, the reaction mixture was filtered through a short plug of silica (eluent DMF) then concentrated *in vacuo* (Genevac^{TM}). Removal of any remaining starting material was achieved via flash column chromatography.

Part B: The residue was then re-dissolved in toluene and treated with *p*-TsOH (0.1 eq). The resultant mixture was heated at reflux under Dean-Stark conditions for 5 h before being allowed to cool to rt. Addition of sat. aq. $NaHCO_3$ solution, followed by extraction with two portions of EtOAc gave an organic solution which was dried over $MgSO_4$, filtered and concentrated *in vacuo*.

2-Methyl-2-(3'-oxobutyl)cyclopentane-1,3-dione 9

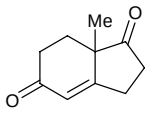


Following *General procedure 1*, Et_3N (3.72 mL, 26.7 mmol), 2-methylcyclopentane-1,3-dione (2.00 g, 17.8 mmol) in EtOAc (400 mL) and methyl vinyl ketone (2.22 mL, 26.7 mmol) gave triketone **9**. Purification of the residue via flash column chromatography (eluent 3:1 30-40 petrol:Et_2O) gave triketone **9** (2.68 g, 82 %) as a pale yellow oil;[2] ν_{max}/cm^{-1} (thin film) 1718 (C=O), 1703 (C=O); δ_H (400 MHz, $CDCl_3$) 1.04 (3H, s, C(2)CH_3), 1.78-1.83 (2H, m, C(1')H_2), 2.04 (3H, s, C(4')H_3), 2.36-2.41 (2H, m, C(2')H_2), 2.64-2.83 (4H, m, C(4)H_2, C(5)H_2); δ_C (100 MHz, $CDCl_3$) 18.9 (C(2)CH$_3$), 27.7 (C(1')H$_2$), 30.0

[2] Triketone **9** has been reported previously but not fully characterised in Z. G. Hajos and D. R. Parish, *J. Org. Chem.*, 1974, **39**, 1615.

(*C*(4')H_3), 34.6 (*C*(4)H_2, *C*(5)H_2), 37.3 (*C*(2')H_2), 55.0 (*C*(2)CH_3), 207.8 (*C*(3')O), 215.8 (C(1)O, C(3)O); *m/z* (CI^+) 183 ($[M+H]^+$, 30 %); HRMS (CI^+) $C_{10}H_{15}O_3$ ($[M+H]^+$) requires 183.1021; found 183.1024.

(*RS*)-7a-Methyl-2,3,7,7a-tetrahydro-6*H*-indene-1,5-dione 11

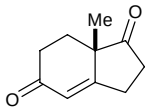


Following *General Procedure 2*, DL-Proline **1** (18 mg, 30 mol%, 0.16 mmol) and triketone **9** (96 mg, 0.52 mmol) in anhydrous DMF (2.0 mL) gave ketol **10**, after 24 h. Purification of the residue via flash column chromatography (eluent Et_2O) furnished ketol (3a*RS*,7a*RS*)-**10** (87 mg, 90 %) as a pale yellow solid;[3] mp 74-76 ºC (lit.,[4] mp 89-91 ºC); ν_{max}/cm^{-1} (KBr disc) 3465 (OH), 1744(C=O), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, s, C(7a)CH_3), 1.63-1.71 (1H, m, C(7)H_AH_B), 1.73-1.82 (1H, m, C(7)H_AH_B), 1.96-2.03 (2H, m, C(2)H_AH_B, C(3)H_AH_B), 2.16 (1H, br s, O*H*), 2.25-2.33 (1H, m, C(6)H_AH_B), 2.36-2.46 (2H, m, C(6)H_AH_B, C(3)H_AH_B), 2.48-2.55 (1H, C(2)H_AH_B), 2.60 (2H, s, C(4)H_2); δ_C (100 MHz, $CDCl_3$) 14.0 (C(7a)*C*H_3), 29.7 (*C*(7)H_2), 32.8 (*C*(2)H_2), 33.5 (*C*(3)H_2), 36.6 (*C*(6)H_2), 50.4 (*C*(4)H_2), 52.6 (*C*(3a)OH), 81.4 (*C*(7a)CH_3), 208.3 (*C*(5)O), 218.3 (*C*(1)O); *m/z* (GC ToF CI^+) 165 ($[M–OH]^+$, 100 %), 183 ($[M+H]^+$, 10); HRMS (GC ToF CI^+) $C_{10}H_{15}O_3$ ($[M+H]^+$) requires 183.1021; found 183.1030. Subsequently, following *General Procedure 2*, a solution of ketol **10** (80 mg, 0.44 mmol) was treated with *p*-TsOH (9 mg, 0.04 mmol) in toluene (4.0 mL). Purification of the residue via flash column chromatography (eluent 1:1 EtOAc, 40-60 petrol) gave enone (*RS*)-**11** (64 mg, 89 %) as a pale yellow solid;[5] mp 52-53 ºC (DCM/Hexane) (lit.,[6] mp 61-63 ºC); ν_{max}/cm^{-1} (KBr disc) 1732 (C(1)=O), 1695 (C(5)=O); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, s, C(7a)CH_3), 1.81-1.91 (1H, m, C(7)H_AH_B), 2.08-2.15 (1H, m, C(7)H_AH_B), 2.39-2.58 (3H, m, C(2)H_AH_B, C(6)H_2), 2.72-2.85 (2H, m, C(2)H_AH_B, C(3)H_AH_B), 2.91-3.02 (1H, m, C(3)H_AH_B), 5.98 (1H, d, *J* 2.3, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 20.6 (C(7a)CH_3), 26.8 (*C*(3)H_2), 29.2 (*C*(7)H_2), 32.9 (*C*(6)H_2), 35.9 (*C*(2)H_2), 48.7 (*C*(7a)CH_3), 123.9 (*C*(4)H), 169.7 (*C*(3a)), 198.1 (*C*(5)O), 216.2 (*C*(1)O); *m/z* (GC ToF CI^+) 165 ($[M+H]^+$, 60 %); HRMS (GC ToF CI^+) $C_{10}H_{13}O_3$ ($[M+H]^+$) requires 165.0916; found 165.0910.

---

[3] Ketol **10** has been reported previously but not fully characterised in Z. G. Hajos and D. R. Parish, *J. Org. Chem.*, 1974, **39**, 1615.
[4] Z. G. Hajos and D. R. Parish, *J. Org. Chem.*, 1974, **39**, 1615.
[5] Enone **11** has previously been reported but not fully characterised in Z. G. Hajos and D. R. Parish, *J. Org. Chem.*, 1974, **39**, 1615.
[6] L. G. Sevillano, C. P. Melero, E. T. F. Caballero, L. G. Lelievre, K. Geering, G. Crambert, R. Carron, M. Medarde and A. S. Feliciano, *J. Med. Chem.*, 2002, **45**, 127.

(*S*)-7a-Methyl-2,3,7,7a-tetrahydro-6*H*-indene-1,5-dione 11



*Catalysis with L-proline **1***: Following *General Procedure 2*, triketone **9** (96 mg, 0.52 mmol) and L-Proline **1** (18 mg, 0.16 mmol) furnished enone (*S*)-**11** in 93 % e.e.[7] (77 mg, 82 %) as a pale yellow solid; mp 52-53 ºC (DCM/Hexane) (lit.,[8] mp 61-63 ºC); $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$), $[\alpha]_D^{22}$ +351 (*c* 0.5 in C_6H_6) {lit.,[9] *ent*. $[\alpha]_D^{24}$ +367 (*c* 1.0 in C_6H_6)}.

*Catalysis with (R)-3-amino-4-phenylbutanoic acid **20***: Following *General Procedure 2*, triketone **9** (106 mg, 0.58 mmol) and (*R*)-3-amino-4-phenylbutanoic acid **20** (31 mg, 0.17 mmol) furnished (*S*)-**11** in 64 % e.e.[7] (70 mg, 73 %) as a pale yellow solid; mp 51-54 ºC (lit.,[8] mp 61-63 ºC); $[\alpha]_D^{22}$ +164.5 (*c* 0.50 in $CHCl_3$) {lit.,[10] $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

*Catalysis with (S)-3-amino-4-methylpentanoic acid **21***: Following *General Procedure 2*, triketone **9** (83 mg, 0.46 mmol) and (*S*)-3-amino-4-methylpentanoic acid **21** (18 mg, 0.14 mmol) furnished enone (*S*)-**11** in 52 % e.e.[7] (51 mg, 69 %) as a pale yellow solid; mp 51-53 ºC (lit.,[8] mp 61-63 ºC); $[\alpha]_D^{22}$ +86.1 (*c* 1.0 in $CHCl_3$) {lit.,[10] $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

*Catalysis with (R)-3-amino-5-methylhexanoic acid **22***: Following *General Procedure 2*, triketone **9** (79 mg, 0.43 mmol) and (*R*)-3-amino-5-methylhexanoic acid **22** (19 mg, 0.13 mmol) furnished (*S*)-**11** in 86 % e.e.[7] (61 mg, 85 %) as a pale yellow solid; mp 52-53 ºC (lit.,[8] mp 61-63 ºC); $[\alpha]_D^{22}$ +194 (*c* 1.0 in $CHCl_3$) {lit.,[10] $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

*Catalysis with (S)-3-amino-3-(o-bromophenyl)propionic acid **32***: Following *General Procedure 2*, triketone **9** (94 mg, 0.52 mmol) and (*S*)-3-amino-3-(*o*-bromophenyl)propionic acid **32** (38 mg, 0.15 mmol) furnished (*S*)-**11** in 48 % e.e.[7] (68 mg, 80 %) as a pale yellow solid; mp 51-53 ºC (lit.,[8] mp 61-63 ºC); $[\alpha]_D^{22}$ +73.2 (*c* 1.2 in $CHCl_3$) {lit.,[10] $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

*Catalysis with (S)-3-amino-3-(o-methoxyphenyl)propionic acid **33***: Following *General Procedure 2*, triketone **9** (95 mg, 0.52 mmol) and (*S*)-3-amino-3-(*o*-methoxyphenyl)propionic acid **33** (31 mg, 0.16

---

[7] The e.e. of enone **11** was determined using chiral GC analysis; ThermoQuest TRACE GC, fitted with a Cydex-β column, 120 ºC isotherm, 120 min and comparison with an authentic racemic sample, (*R*)-**11** t_R = 91.5 min, (*S*)-**11** t_R = 100.5 min.

[8] L. G. Sevillano, C. P. Melero, E. T. F. Caballero, L. G. Lelievre, K. Geering, G. Crambert, R. Carron, M. Medarde and A. S. Feliciano, *J. Med. Chem.*, 2002, **45**, 127.

[9] Z. G. Hajos and D. R. Parish, *J. Org. Chem.*, 1974, **39**, 1615.

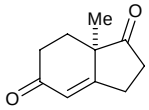
[10] A sample of (*S*)-**11** (93 % e.e.) was prepared under standard conditions using L-proline **1** catalysis.

mmol) furnished (*S*)-**11** in 56 % e.e.[11] (60 mg, 71 %) as a pale yellow solid; mp 52-53 ºC (lit.,[12] mp 61-63 ºC); $[\alpha]_D^{22}$ +111 (*c* 0.8 in $CHCl_3$) {lit.,[13] $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

Catalysis with (S)-3-amino-3-(m-methoxyphenyl)propionic acid ***34***: Following *General Procedure 2*, triketone **9** (81 mg, 0.44 mmol) and (*S*)-3-amino-3-(*m*-methoxyphenyl)propionic acid **34** (26 mg, 0.13 mmol) furnished (*S*)-**11** in 37 % e.e.[11] (19 mg, 26 %) as a pale yellow solid; mp 52-53 ºC (lit.,[12] mp 61-63 ºC); $[\alpha]_D^{22}$ +30.6 (*c* 0.5 in $CHCl_3$) {lit.,[13] $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

Catalysis with (S)-3-amino-3-(m-fluorophenyl)propanoic acid ***35***: Following *General Procedure 2*, triketone **9** (68 mg, 0.37 mmol) and (*S*)-3-amino-3-(3'-fluorophenyl)propanoic acid **35** (21 mg, 0.12 mmol) furnished (*S*)-**11** in 72 % e.e.[11] (50 mg, 79 %) as a pale yellow solid; mp 52-53 ºC (lit.,[12] mp 61-63 ºC); $[\alpha]_D^{22}$ +162 (*c* 1.8 in $CHCl_3$) {lit.,[13] $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

(*R*)-7a-Methyl-2,3,7,7a-tetrahydro-6*H*-indene-1,5-dione 11



Catalysis with (S)-3-aminobutanoic acid ***19***: Following *General Procedure 2*, triketone **9** (113 mg, 0.62 mmol) and (*S*)-3-aminobutanoic acid **19** (19 mg, 0.19 mmol) furnished (*R*)-**11** in 47 % e.e.[11] (15 mg, 15 %) as a pale yellow solid; mp 52-53 ºC (lit.,[12] mp 61-63 ºC); $[\alpha]_D^{22}$ –51.7 (*c* 1.0 in $CHCl_3$) {lit.,[13] *ent*. $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

Catalysis with (S)-3-(N-methylamino)butanoic acid ***23***: Following *General Procedure 2*, triketone **9** (124 mg, 0.68 mmol) and (*S*)-3-(*N*-methylamino)butanoic acid **23** (24 mg, 0.20 mmol) furnished (*R*)-**11** in 11 % e.e.[11] (11 mg, 10 %) as a pale yellow solid; mp 52-53 ºC (lit.,[12] mp 61-63 ºC); $[\alpha]_D^{22}$ –1.6 (*c* 0.5 in $CHCl_3$) {*ent*.[13] $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

Catalysis with (S)-3-(N-benzylamino)-butanoic acid ***24***: Following *General Procedure 2*, triketone **9** (79 mg, 0.43 mmol) and (*S*)-3-(*N*-benzylamino)butanoic acid **24** (25 mg, 0.13 mmol) produced a 6:94 mixture of **10** and starting material **9** respectively. The e.e. of **10** was not determined in this case.

---

[11] The e.e. of enone **11** was determined using chiral GC analysis; ThermoQuest TRACE GC, fitted with a Cydex-β column, 120 ºC isotherm, 120 min and comparison with an authentic racemic sample, (*R*)-**11** t_R = 91.5 min, (*S*)-**11** t_R = 100.5 min.

[12] L. G. Sevillano, C. P. Melero, E. T. F. Caballero, L. G. Lelievre, K. Geering, G. Crambert, R. Carron, M. Medarde and A. S. Feliciano, *J. Med. Chem.*, 2002, **45**, 127.

[13] A sample of (*S*)-**11** (93 % e.e.) was prepared under standard conditions using L-proline **1** catalysis.

*Attempted catalysis with (3S,αS)-3-[N-(α-methylbenzyl)amino]butanoic acid **25***: Following *General Procedure 2*, triketone **9** (113 mg, 0.62 mmol) and (3*S*,α*S*)-3-[*N*-(α-methylbenzyl)amino]butanoic acid **25** (38 mg, 0.19 mmol) gave only returned starting material **9** (67 mg, 59 %).

*Catalysis with (S)-homoproline **26***: Following *General Procedure 2*, triketone **9** (110 mg, 0.60 mmol) and (*S*)-homoproline **26** (23 mg, 0.18 mmol) furnished (*R*)-**11** in 36 % e.e.[14] (63 mg, 64 %) as a pale yellow solid; mp 51-53 ºC (lit.,[15] mp 61-63 ºC); $[\alpha]_D^{22}$ –30.0 (*c* 1.0 in $CHCl_3$) {lit.,[16] *ent*. $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

*Catalysis with (R)-3-amino-3-phenylpropionic acid **27***: Following *General Procedure 2*, triketone **9** (85 mg, 0.46 mmol) and (*R*)-3-amino-3-phenylpropanonic acid **27** (23 mg, 0.14 mmol) furnished (*R*)-**11** in 40 % e.e.[14] (28 mg, 36 %) as a pale yellow solid; mp 52-54 ºC (lit.,[15] mp 61-63 ºC); $[\alpha]_D^{22}$ –44.0 (*c* 1.0 in $CHCl_3$) {lit.,[16] *ent*. $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

*Catalysis with (R)-3-amino-3-(o-iodophenyl)propanoic acid **28***: Following *General Procedure 2*, triketone **9** (63 mg, 0.35 mmol) and (*R*)-3-amino-3-(*o*-iodophenyl)propanoic acid **28** (30 mg, 0.10 mmol) furnished (*R*)-**11** in 81 % e.e.[14] (25 mg, 44 %) as a pale yellow solid; mp 52-53 ºC (lit.,[15] mp 61-63 ºC); $[\alpha]_D^{22}$ −216 (*c* 1.2 in $CHCl_3$) {lit.,[16] *ent*. $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

*Catalysis with (R)-3-amino-3-(m-hydroxyphenyl)propanoic acid **29***: Following *General Procedure 2*, triketone **9** (82 mg, 0.45 mmol) and (*R*)-3-amino-3-(*m*-hydroxyphenyl)propanoic acid **29** (24 mg, 0.13 mmol) furnished (*R*)-**11** in 49 % e.e.[14] (28 mg, 45 %) as a pale yellow solid; mp 53-54 ºC (lit.,[15] mp 61-63 ºC); $[\alpha]_D^{22}$ −131 (*c* 1.4 in $CHCl_3$) {lit.,[16] *ent*. $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

*Catalysis with (R)-3-amino-3-(p-hydroxyphenyl)propanoic acid **30***: Following *General Procedure 2*, triketone **9** (78 mg, 0.43 mmol) and (*R*)-3-amino-3-(*p*-hydroxyphenyl)propanoic acid **30** (23 mg, 0.13 mmol) furnished (*R*)-**11** in 48 % e.e.[14] (35 mg, 50 %) as a pale yellow solid; mp 52-53 ºC (lit.,[15] mp 61-63 ºC); $[\alpha]_D^{22}$ −92 (*c* 1.0 in $CHCl_3$) {lit.,[16] *ent*. $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

*Catalysis with (R)-3-amino-3-(m,p-dimethoxyphenyl)propanoic acid **31***: Following *General Procedure 2*, triketone **9** (79 mg, 0.43 mmol) and (*R*)-3-amino-3-(*m,p*-dimethoxyphenyl)propanoic acid **31** (29 mg,

---

[14] The e.e. of enone **11** was determined using chiral GC analysis; ThermoQuest TRACE GC, fitted with a Cydex-β column, 120 ºC isotherm, 120 min and comparison with an authentic racemic sample, (*R*)-**11** t_R = 91.5 min, (*S*)-**11** t_R = 100.5 min.

[15] L. G. Sevillano, C. P. Melero, E. T. F. Caballero, L. G. Lelievre, K. Geering, G. Crambert, R. Carron, M. Medarde and A. S. Feliciano, *J. Med. Chem.*, 2002, **45**, 127.

[16] A sample of (*S*)-**11** (93 % e.e.) was prepared under standard conditions using L-proline **1** catalysis.

0.13 mmol) furnished (*R*)-**11** in 43 % e.e.[17] (48 mg, 67 %) as a pale yellow solid; mp 53-55 ºC (lit.,[18] mp 61-63 ºC); $[\alpha]_D^{22}$ −84 (*c* 1.2 in $CHCl_3$) {lit.,[19] *ent*. $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

*Catalysis with (S)-2-(aminomethyl)butanoic acid **36***: Following *General Procedure 2*, triketone **9** (75 mg, 0.41 mmol) and (*S*)-2-(aminomethyl)butanoic acid **36** (14 mg, 0.12 mmol) furnished (*R*)-**11** in 26 % e.e.[17] (26 mg, 39 %) as a pale yellow solid; mp 51-52 ºC (lit.,[18] mp 61-63 ºC); $[\alpha]_D^{22}$ –63.2 (*c* 0.8 in $CHCl_3$) {lit.,[19] $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

*Catalysis with (S)-2-(aminomethyl)-3-methylbutanoic acid **37***: Following *General Procedure 2*, triketone **9** (77 mg, 0.42 mmol) and (*S*)-2-(aminomethyl)-3-methylbutanoic acid **37** (17 mg, 0.13 mmol) furnished (*R*)-**11** in 56 % e.e.[17] (61 mg, 88 %) as a pale yellow solid; mp 52-53 ºC (lit.,[18] mp 61-63 ºC); $[\alpha]_D^{22}$ –125 (*c* 1.1 in $CHCl_3$) {lit.,[19] $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

*Catalysis with (1R,2S)-cispentacin **38***: Following *General Procedure 2*, triketone **9** (124 mg, 0.68 mmol) and (1*R*,2*S*)-cispentacin **38** (26 mg, 0.20 mmol) furnished (*R*)-**11** in 90 % e.e.[17] (104 mg, 94 %) as a pale yellow solid; mp 52-54 ºC (lit.,[18] mp 61-63 ºC); $[\alpha]_D^{22}$ –282 (*c* 1.0 in $CHCl_3$) {lit.,[19] *ent*. $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

*Catalysis with (1R,2S)-cishexacin **39***: Following *General Procedure 2*, triketone **9** (106 mg, 0.58 mmol) and (1*R*,2*S*)-cishexacin **39** (25 mg, 0.17 mmol) furnished (*R*)-**11** in 87 % e.e.[17] (88 mg, 92 %) as a pale yellow solid; mp 52-53 ºC (lit.,[18] mp 61-63 ºC); $[\alpha]_D^{22}$ –170.6 (*c* 1.0 in $CHCl_3$) {lit.,[19] *ent*. $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

*Catalysis with (1S,2S)-transpentacin **40***: Following *General Procedure 2*, triketone **9** (99 mg, 0.54 mmol) and (1*S*,2*S*)-transpentacin **40** (21 mg, 0.16 mmol) furnished (*R*)-**11** in 66 % e.e.[17] (82 mg, 92 %) as a pale yellow solid; mp 52-54 ºC (lit.,[18] mp 61-63 ºC); $[\alpha]_D^{22}$ –103.4 (*c* 1.0 in $CHCl_3$) {lit.,[19] *ent*. $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

*Catalysis with (1S,2S)-transhexacin **41***: Following *General Procedure 2*, triketone **9** (95 mg, 0.52 mmol) and (1*S*,2*S*)-transhexacin **41** (22 mg, 0.16 mmol) furnished (*R*)-**11** in 63 % e.e.[17] (74 mg, 87 %) as a pale yellow solid; mp 53-54 ºC (lit.,[18] mp 61-63 ºC); $[\alpha]_D^{22}$ –105.9 (*c* 1.0 in $CHCl_3$) {lit.,[19] *ent*.$[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

---

[17] The e.e. of enone **11** was determined using chiral GC analysis; ThermoQuest TRACE GC, fitted with a Cydex-β column, 120 ºC isotherm, 120 min and comparison with an authentic racemic sample, (*R*)-**11** t_R = 91.5 min, (*S*)-**11** t_R = 100.5 min.

[18] L. G. Sevillano, C. P. Melero, E. T. F. Caballero, L. G. Lelievre, K. Geering, G. Crambert, R. Carron, M. Medarde and A. S. Feliciano, *J. Med. Chem.*, 2002, **45**, 127.

[19] A sample of (*S*)-**11** (93 % e.e.) was prepared under standard conditions using L-proline **1** catalysis.

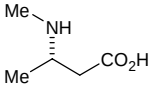
Catalysis with (1R,2S,3R)-3-methyl cispentacin ***42***: Following *General Procedure 2*, triketone **9** (84 mg, 0.46 mmol) and (1*R*,2*S*,3*R*)-3-methyl cispentacin **42** (20 mg, 0.14 mmol) furnished (*R*)-**11** in 90 % e.e.[20] (66 mg, 87 %) as a pale yellow solid; mp 52-53 ºC (lit.,[21] mp 61-63 ºC); $[\alpha]_D^{22}$ −223 (*c* 1.0 in $CHCl_3$) {lit.,[22] *ent*. $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

Catalysis with (1R,2S,3R)-3-ethyl cispentacin ***43***: Following *General Procedure 2*, triketone **9** (93 mg, 0.51 mmol) and (1*R*,2*S*,3*R*)-3-ethyl cispentacin **43** (24 mg, 0.15 mmol) furnished (*R*)-**11** in 84 % e.e.[20] (77 mg, 92 %) as a pale yellow solid; mp 52-53 ºC (lit.,[21] mp 61-63 ºC); $[\alpha]_D^{22}$ −210 (*c* 1.0 in $CHCl_3$) {lit.,[22] *ent*. $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

Catalysis with (1R,2S,3S)-3-benzyl cispentacin ***44***: Following *General Procedure 2*, triketone **9** (95 mg, 0.52 mmol) and (1*R*,2*S*,3*S*)-3-benzyl cispentacin **44** (34 mg, 0.16 mmol) furnished (*R*)-**11** in 88 % e.e.[20] (76 mg, 90 %) as a pale yellow solid; mp 53-55 ºC (lit.,[21] mp 61-63 ºC); $[\alpha]_D^{22}$ −173 (*c* 1.0 in $CHCl_3$) {lit.,[22] *ent*. $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

Catalysis with (3S,4R)-4-aminotetrahydrofuran-3-carboxylic acid ***45***: Following *General Procedure 2*, triketone **9** (74 mg, 0.40 mmol) and (3*S*,4*R*)-4-aminotetrahydrofuran-3-carboxylic acid **45** (16 mg, 0.12 mmol) furnished (*R*)-**11** in 86 % e.e.[20] (57 mg, 86 %) as a pale yellow solid; mp 53-54 ºC (lit.,[21] mp 61-63 ºC); $[\alpha]_D^{22}$ −230 (*c* 1.0 in $CHCl_3$) {lit.,[22] *ent*. $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}.

(*S*)-3-(*N*-methylamino)butanoic acid 23



BuLi (3.39 mL, 5.43 mmol) was added to a solution of (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amine (756 mg, 5.60 mmol) in anhydrous THF (50 mL) at –78 °C. After 30 min, a solution of *tert*-butyl crotonate (498 mg, 3.50 mmol) in THF (20 mL), also at –78 °C, was added. The resultant mixture was stirred for 2 h before addition of sat. aq. NH_4Cl solution (10 mL). The resultant mixture was allowed to warm to rt and concentrated *in vacuo*. The residue was re-dissolved in Et_2O and the resultant organic solution was sequentially washed with 10 % aq. citric acid solution, brine, sat. aq. $NaHCO_3$ solution an once more with brine then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue via flash

[20] The e.e. of enone **11** was determined using chiral GC analysis; ThermoQuest TRACE GC, fitted with a Cydex-β column, 120 ºC isotherm, 120 min and comparison with an authentic racemic sample, (*R*)-**11** t_R = 91.5 min, (*S*)-**11** t_R = 100.5 min.

[21] L. G. Sevillano, C. P. Melero, E. T. F. Caballero, L. G. Lelievre, K. Geering, G. Crambert, R. Carron, M. Medarde and A. S. Feliciano, *J. Med. Chem.*, 2002, **45**, 127.

[22] A sample of (*S*)-**11** (93 % e.e.) was prepared under standard conditions using L-proline **1** catalysis.

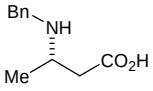
column chromatography (eluent 6:1 30-40 petrol:Et_2O) yielded *tert*-butyl (3*S*,α*S*)-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]butanoate (1.23 g, 90 %) as a pale yellow oil; $[\alpha]_D^{22}$ +8.9 (*c* 0.8 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.8, C(4)H_3), 1.34 (3H, d, *J* 6.6, C(α)HCH_3), 1.45 (9H, s, C(CH_3)$_3$), 2.07 (3H, s, NCH_3), 2.16 (1H, dd, *J* 13.9, 7.8, C(2)H_AH$_B$), 2.45 (1H, dd, *J* 13.9, 6.8, C(2)H$_A$$H_B$), 3.46-3.51 (1H, m, C(3)*H*), 3.56 (1H, q, *J* 6.6, C(α)*H*), 7.19-7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3 (*C*(4)H$_3$), 21.7 (C(α)H*C*H$_3$), 28.1 (C(*C*H$_3$)$_3$), 32.1 (N*C*H$_3$), 40.1 (*C*(2)H$_2$), 51.2 (*C*(3)H), 62.0 (*C*(α)H), 79.9 (*C*(CH$_3$)$_3$), 126.6, 127.2, 128.2 (*o*,*m*,*p*-*Ph*), 146.2 (*i*-*Ph*), 168.0 (*C*O^{t}Bu); *m/z* (ESI$^+$) 278 ([M+H]$^+$, 100 %); HRMS (ESI$^+$) $C_{17}H_{28}NO_2$ ([M+H]$^+$) requires 278.2120; found 278.2122.

P(OH)$_2$/C (308 mg, 25 % w/w), was added to a degassed solution of *tert*-butyl (3*S*,α*S*)-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]butanoate (1.23 g, 4.4 mmol) in MeOH:H_2O:AcOH (5.0:0.5:0.125 mL). The resultant mixture was stirred under hydrogen (1 atm) for 16 h before being filtered through celite® (eluent MeOH). The resultant solution was concentrated *in vacuo* and the residue was re-dissolved in DCM. The organic solution was then sequentially washed with sat. aq. $NaHCO_3$ solution and brine before being dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield *tert*-butyl (*S*)-3-(*N*-methylamino)butanoate (762 mg, quant) as a colourless oil; $[\alpha]_D^{22}$ +1.0 (*c* 1.3 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.5, C(4)H_3), 1.46 (9H, s, C(CH_3)$_3$), 1.54 (1H, br, app s, N*H*), 2.24 (1H, dd, *J* 15.0, 5.8, C(2)H_AH$_B$), 2.39 (1H, dd, *J* 15.0, 6.8, C(2)H$_A$$H_B$), 2.41 (3H, s, NC$H_3$), 2.91-3.00 (1H, m, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 19.9 (*C*(4)H$_3$), 28.1 (C(*C*H$_3$)$_3$), 33.7 (N*C*H$_3$), 42.4 (*C*(2)H$_2$), 52.0 (*C*(3)H), 80.4 (*C*(CH$_3$)$_3$), 171.8 (*C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 347 ([2M+H]$^+$, 80 %), 174 ([M+H]$^+$, 50); HRMS (ESI$^+$) $C_9H_{20}NO_2$ ([M+H]$^+$) requires 174.1494; found 174.1491.

tert-Butyl (*S*)-3-(*N*-methylamino)butanoate (300 mg, 1.73 mmol) was subsequently treated with TFA:DCM (2:2 mL) at rt for 16 h before beinng concentrated *in vacuo*. Purification of the residue via ion exchange chromatography (Dowex 50Wx8 200, eluent 1.0 M NH_4OH aq.) furnished β-amino acid (*S*)-**23** (168 mg, 83 %) as a white solid; mp 180-184 ºC; $[\alpha]_D^{22}$ +17.4 (*c* 1.1 in H_2O); ν_{max}/cm^{-1} (KBr disc) 1720 (C=O); δ_H (400 MHz, MeOD) 1.36 (3H, d, *J* 6.8, C(4)H_3), 2.49 (1H, dd, *J* 16.9, 7.2, C(2)H_AH$_B$), 2.58 (1H, dd, *J* 16.9, 5.1, C(2)H$_A$$H_B$), 2.71 (3H, s, NC$H_3$), 3.39-3.48 (1H, m, C(3)*H*); δ_C (100 MHz, MeOD) 15.5 (*C*(4)H$_3$), 29.4 (N*C*H$_3$), 38.0 (*C*(2)H$_2$), 53.2 (*C*(3)H), 175.7 (*C*O$_2$H); *m/z* (ESI$^+$) 257 ([2M+Na]$^+$, 90 %), 235 ([2M+H]$^+$, 100), 140 ([M+Na]$^+$, 20), 118 ([M+H]$^+$, 20).[23]

[23] Repeated attempts at accurate mass determination for **23** were unsuccessful due to significant dimerisation of molecular ions.

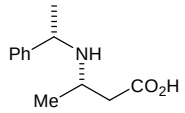
(*S*)-3-(*N*-Benzylamino)butanoic acid 24



BuLi (3.06 mL, 4.91 mmol) was added to a solution of (*S*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amine (1.22 g, 5.06 mmol) in anhydrous THF (50 mL) at –78 °C. After 30 min, a solution of *tert*-butyl crotonate (450 mg, 3.16 mmol) in THF (20 mL), also at –78 °C, was added. The resultant mixture was stirred for 2 h before addition of sat. aq. NH_4Cl solution (10 mL). The resultant mixture was allowed to warm to rt and concentrated *in vacuo*. The residue was re-dissolved in Et_2O and the resultant organic solution was sequentially washed with 10 % aq. citric acid solution, brine, sat. aq. $NaHCO_3$ solution an once more with brine then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue via flash column chromatography (eluent 1:1 30-40 petrol:Et_2O) afforded *tert*-butyl (3*S*,α*S*)-3-[*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]butanoate (1.20 g, 99 %) as a pale yellow oil; $[\alpha]_D^{24}$ –7.8 (*c* 1.6 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 1718 (C=O); δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.6, C(4)H_3), 1.34 (3H, d, *J* 6.8, C(α)HCH_3), 1.43 (9H, s, C(CH_3)$_3$), 2.04 (1H, dd, *J* 14.1, 9.0, C(2)H_AH$_B$), 2.27 (1H, dd, *J* 14.1, 4.5, C(2)H$_A$$H_B$), 3.41-3.49 (1H, m, C(3)*H*), 3.61 (1H, d, *J* 15.0, NCH_AH$_B$Ph), 3.75 (1H, d, *J* 15.0, NCH$_A$$H_B$Ph), 3.81 (3H, s, ArOC$H_3$), 3.87 (1H, q, *J* 6.8, C(α)*H*), 6.83-6.87 (2H, m, *Ar*), 7.21-7.43 (7H, m, 2 × *Ar*, 5 × *Ph*); δ_C (100 MHz, $CDCl_3$) 18.5 (*C*(4)H$_3$), 19.2 (C(α)H*C*H$_3$), 28.1 (C(*C*H$_3$)$_3$), 40.6 (*C*(2)H$_2$), 49.6 (N*C*H$_2$Ph), 50.1 (*C*(3)H), 55.2 ArO*C*H$_3$), 57.7 (*C*(α)HCH$_3$), 79.9 (*C*(CH$_3$)$_3$), 113.4, 113.4 (2 × *Ar*), 126.4, 128.1, 128.1, 128.7 (2 × *Ar*, 5 × *o*,*m*,*p*-*Ph*), 136.4 (CH$_3$O*C*CH), 142.2 (NCH(CH$_3$)*C*CH), 158.3 (*i*-*Ph*), 172.0 (*C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 384 ([M+H]$^+$, 100 %); HRMS (ESI$^+$) $C_{24}H_{34}NO_3$ ([M+H]$^+$) requires 384.2539; found 384.2539.

tert-Butyl (3*S*,α*S*)-3-[*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]butanoate (430 mg, 1.12 mmol) was treated with TFA:DCM (5:5 mL) at rt for 16 h before being concentrated *in vacuo*. Purification of the residue via ion exchange chromatography (Dowex 50Wx8 200, eluent 1.0 M NH_4OH aq.) furnished β-amino acid (*S*)-**24** (145 mg, 67 %) as a white solid; mp 163-164 ºC; $[\alpha]_D^{22}$ +20.8 (*c* 1.0 in H_2O); ν_{max}/cm^{-1} (KBr disc) 1720 (C=O); δ_H (400 MHz, MeOD) 1.39 (3H, dd, *J* 6.6, 1.5, C(4)H_3), 2.42 (1H, ddd, *J* 16.7, 8.1, 1.5, C(2)H_AH$_B$), 2.57 (1H, ddd, *J* 16.7, 4.3, 1.5, C(2)H$_A$$H_B$), 3.45-3.54 (1H, m, C(3)*H*), 4.18 (1H, d, *J* 13.0, CH_AH$_B$Ph), 4.28 (1H, d, *J* 13.0, CH$_A$$H_B$Ph), 7.42-7.53 (5H, m, *Ph*); δ_C (100 MHz, MeOD) 16.0 (*C*(4)H$_3$), 38.3 (*C*(2)H$_2$), 48.1 (N*C*H$_2$Ph), 52.1 (*C*(3)H), 129.3, 129.4, 129.6 (*o*,*m*,*p*-*Ph*), 132.4 (*i*-*Ph*), 176.8 (*C*O$_2$H); *m/z* (ESI$^+$) 387 ([2M+H]$^+$, 100 %), 194 ([M+H]$^+$, 60); HRMS (ESI$^+$) $C_{11}H_{16}NO_2$ ([M+H]$^+$) requires 194.1181; found 194.1189.

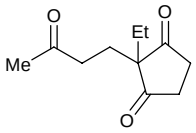
(3*S*,α*S*)-3-[*N*-(α-methylbenzyl)amino]butanoic acid 25



CAN (4.57 g, 8.34 mmol) was added in one portion to a solution of *tert*-butyl (3*S*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate (980 mg, 2.78 mmol) in MeCN:H_2O (75:25 mL) at rt. The reaction mixture was stirred for 16 h before addition of sat. aq. K_2CO_3 solution (50 mL). The resultant mixture was extracted with two portions of DCM then the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield *tert*-butyl (3*S*,α*S*)-3-[*N*-(α-methylbenzyl)amino]butanoate (730 mg, 99 %) as a colourless oil; $[\alpha]_D^{22}$ –37.0 (*c* 1.5 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.6, C(4)H_3), 1.33 (3H, d, *J* 6.6, C(α)HCH_3), 1.46 (9H, s, C(CH_3)$_3$), 2.30 (1H, dd, *J* 14.4, 6.1, C(2)H_AH$_B$), 2.36 (1H, dd, *J* 14.4, 5.6, C(2)H$_A$$H_B$), 2.92-3.00 (1H, m, C(3)*H*), 3.90 (1H, app q, *J* 6.6, C(α)*H*), 7.21-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.3 (*C*(4)H$_3$), 24.5 (C(α)H*C*H$_3$), 28.1 (C(*C*H$_3$)$_3$), 41.9 (*C*(2)H$_2$), 48.1 (*C*(3)H), 55.2 (*C*(α)H), 80.3 (*C*(CH$_3$)$_3$), 126.6, 126.8, 128.4 (*o*,*m*,*p*-*Ph*), 146.0 (*i*-*Ph*), 171.7 (*C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 264 ([M+H]$^+$, 100 %); HRMS (ESI$^+$) $C_{16}H_{26}NO_2$ ([M+H]$^+$) requires 264.1964; found 264.1967.

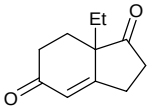
tert-Butyl (3*S*,α*S*)-3-[*N*-(α-methylbenzyl)amino]butanoate (740 mg, 2.81 mmol) was subsequently treated with TFA:DCM (10:10 mL) at rt for 16 h before being concentrated *in vacuo*. Purification of the residue via ion exchange chromatography of the residue (Dowex 50Wx8 200, 1.0 M NH_4OH aq. eluent) furnished β-amino acid (3*S*,α*S*)-**25** (390 mg, 67 %) as a white solid; mp 243 ºC; $[\alpha]_D^{22}$ +10.9 (*c* 0.8 in H_2O); ν_{max}/cm^{-1} (KBr disc) 1718 (C=O); δ_H (500 MHz, MeOD) 1.32 (3H, d, *J* 6.6, C(4)H_3), 1.70 (3H, d, *J* 6.7, C(α)HCH_3), 2.46 (1H, dd, *J* 16.7, 6.8, C(2)H_AH$_B$), 2.61 (1H, dd, *J* 16.7, 5.4, C(2)H$_A$$H_B$), 3.44-3.49 (1H, m, C(3)*H*), 4.54 (1H, app q, *J* 6.8, C(α)*H*), 7.44-7.57 (5H, m, *Ph*); δ_C (125 MHz, MeD) 16.5 (*C*(4)H$_3$), 18.9 (C(α)H*C*H$_3$), 37.8 (*C*(2)H$_2$), 50.2 (*C*(3)H), 55.6 (*C*(α)H), 127.4, 129.5, 129.6 (*o*,*m*,*p*-*Ph*), 137.8 (*i*-*Ph*), 176.0 (*C*O$_2$H); *m/z* (ESI$^+$) 208 ([M+H]$^+$, 100 %); HRMS (ESI$^+$) $C_{12}H_{18}NO_2$ ([M+H]$^+$) requires 208.1338; found 208.1333.

2-Ethyl-2-(3'-oxobutyl)cyclopenta-1,3-dione 46



Following *General Procedure 1*, Et_3N (1.66 mL, 11.9 mmol), 2-ethylcyclopenta-1,3-dione (1.00 g, 7.93 mmol) and methyl vinyl ketone (0.99 mL, 11.9 mmol) in EtOAc (200 mL) furnished triketone **46** (1.02 g, 66 %) as a pale yellow oil after flash column chromatography (eluent 2:1 Et_2O:30-40 petrol);[24] ν_{max}/cm^{-1} (thin film) 1760 (C=O), 1718 (C=O); δ_H (400 MHz, $CDCl_3$) 0.79 (3H, t, *J* 7.4, CH_2CH_3), 1.65 (2H, q, *J* 7.4, CH_2CH_3), 1.88 (2H, t, *J* 7.3, C(1')H_2), 2.09 (3H, s, C(4')H_3), 2.42 (2H, t, *J* 7.3, C(2')H_2), 2.63-2.87 (4H, m, C(4)H_2, C(5)H_2); δ_C (100 MHz, $CDCl_3$) 8.8 (CH_2CH_3), 26.4 (*C*(1')H_2), 28.1 (CH_2CH_3), 30.0 (C(4')H_3), 35.6 (*C*(4)H_2, *C*(5)H_2), 37.6 (*C*(2')H_2), 59.7 (*C*(2)Et), 208.0 (*C*(3')O), 216.2 (*C*(1)O, *C*(3)O); *m/z* (GC ToF CI^+) 214 ($[M+NH_4]^+$, 100 %); HRMS (GC ToF CI^+) $C_{11}H_{20}NO_3$ ($[M+NH_4]^+$) requires 214.1443 found 214.1434.

(*RS*)-7a-Ethyl-2,3,7,7a-tetrahydro-(6*H*)-indene-1,5-dione 47



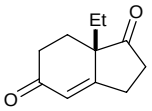
Following *General Procedure 2*, DL-proline **1** (26 mg, 0.23 mmol) was added to triketone **46** (150 mg, 0.76 mmol) in anhydrous DMF (2.0 mL). After 1 day the reaction was worked-up to furnish a 50:50 mixture of triketone **46** and ketol **63** respectively (110 mg, 73 %) as a pale orange oil. Following *General Procedure 2*, this mixture was treated with *p*-TsOH (11 mg, 0.06 mmol) in toluene (4.0 mL) to furnish enone **47** (80 mg, 80 %) as a brown oil;[25] ν_{max}/cm^{-1} (thin film) 1742 (C(1)=O), 1667 (C(5)=O), 1614 (C=C); δ_H (400MHz, $CDCl_3$) 0.97 (3H, t, *J* 7.5, CH_2CH_3), 1.69-1.81 (3H, m, CH_2CH_3, C(7)H_AH_B), 2.23-2.29 (1H, m, C(7)H_AH_B), 2.36-2.46 (3H, m, C(2)H_AH_B, C(6)H_2), 2.66-2.83 (2H, m, C(2)H_AH_B, C(3)H_AH_B), 2.92-3.02 (1H, m, C(3)H_AH_B), 5.97 (1H, s, C(4)*H*); δ_C (100MHz, $CDCl_3$) 8.9 (CH_2CH_3), 25.7 (*C*(7)H_2), 26.9, 27.0 (CH_2CH_3, *C*(3)H_2), 32.6 (*C*(6)H_2), 35.8 (*C*(2)H_2), 52.6 (*C*(7a)Et), 124.1 (*C*(4)H), 170.2 (*C*(3a)OH), 198.2 (*C*(1)O), 215.9 (*C*(5)O); *m/z* (GC ToF CI^+) 179 ($[M+H]^+$, 100%); HRMS (GC ToF CI^+) $C_{11}H_{15}O_2$ ($[M+H]^+$) requires 179.1072 found 179.1076.

---

[24] Triketone **46** has previously been reported but not fully characterized in Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1612.

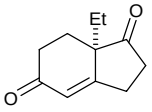
[25] Enone **47** has previously been reported but not fully characterized in Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1615.

Preparation of (*S*)-7a-Ethyl-2,3,7,7a-tetrahydro-(6*H*)-indene-1,5-dione 47



Following *General Procedure 2*, L-proline **1** (26 mg, 0.23 mmol) was added to triketone **46** (150 mg, 0.76 mmol) in anhydrous DMF (2.0 mL). After 11 days the reaction was worked-up to furnish ketol **63** (116 mg, 77 %) as a pale orange oil;[26] $[\alpha]_D^{21}$ +18.9 (*c* 0.55 in $CHCl_3$) {lit.,[27] $[\alpha]_D^{25}$ +18.9 (*c* 1.0, $CHCl_3$)}; ν_{max}/cm^{-1} (thin film) 3046 (O–H), 1743 (C=O), 1667 (C=O); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, t, *J* 7.4, CH_2CH_3), 1.63-1.74 (1H, m, C(7)H_AH_B), 1.74-1.85 (2H, m, CH_2CH_3) 1.92-2.01 (1H, m, C(3)H_AH_B) 2.05-2.18 (2H, m, C(3)H_AH_B, C(6)H_AH_B) 2.22-2.32 (2H, m, C(6)H_AH_B, C(7)H_AH_B), 2.33-2.47 (1H, m, C(2)H_AH_B), 2.49-2.52 (2H, m, C(4)H_2), 2.53-2.62 (1H, m, C(2)H_AH_B); δ_C (100 MHz, $CDCl_3$) 8.3 (CH_3CH_2), 22.8 (CH_3CH_2), 25.8 (C(7)H_2), 33.3 (C(3)H_2), 34.3 (C(2)H_2), 37.1 (C(6)H_2), 51.1 (C(4)H_2), 55.2 (C(7a)Et), 82.4 (C(3a)OH), 209.2 (C(5)O), 217.2 (C(1)O); *m/z* (FI^+) 196($[M]^+$, 100 %); HRMS (FI^+) $C_{11}H_{16}O_3$ ($[M]^+$) requires 196.1099 found 196.1094. Following *General Procedure 2*, ketol **63** (50 mg, 0.26 mmol) and *p*-TsOH (5 mg, 0.03 mmol) in toluene (2.0 mL) furnished enone (*S*)-**47** (40 mg, 88 %) in 74 % e.e., [28] as a brown oil; $[\alpha]_D^{21}$ +154.3 (*c* 1.05 in $CHCl_3$).

(*R*)-7a-Ethyl-2,3,7,7a-tetrahydro-(6*H*)-indene-1,5-dione 47



Following *General Procedure 2*, (1*R*,2*S*)-cispentacin **38** (20 mg, 0.15 mmol) was added to triketone **46** (100 mg, 0.51 mmol) in anhydrous DMF (2.0 mL). After 4.5 days a 1.0 mL aliquot was removed and worked-up to furnish ketol **63** (39 mg, 78 %) as a pale yellow solid. This material (39 mg, 0.20 mmol) was immediately dehydrated according to *General Procedure 2*, with *p*-TsOH (4 mg, 0.02 mmol) in toluene (1.0 mL) to furnish enone (*R*)-**47** in 78 % e.e.,[28] (28 mg, 79 %) as a brown oil; $[\alpha]_D^{23}$ –19.2 (*c* 0.25 in $CHCl_3$).

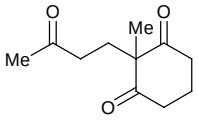
---

[26] Ketol **63** has previously been reported but not fully characterized in Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1615.

[27] R. A. Michelli, Z. G. Hajos, N. Cohen, D. R. Parrish, L. A. Portland, W. Sciamanna, M. A. Scott and P. A. Wehrli, *J. Org. Chem.*, 1975, **40**, 675.

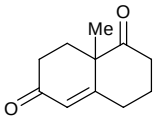
[28] The e.e. of enone **47** was determined using chiral GC analysis; ThermoQuest TRACE GC, fitted with a Cydex-β column, 130 ºC isotherm, 120 min and comparison with an authentic racemic sample, (*R*)-**47** t_R = 85.0 min, (*S*)-**47** t_R = 88.2 min.

2-Methyl-2-(3'-oxobutyl)cyclohexa-1,3-dione 48



Following *General Procedure 1*, Et_3N (1.66 mL, 11.9 mmol), 2-methylcyclohexa-1,3-dione (1.00 g, 7.93 mmol) and methyl vinyl ketone (0.99 mL, 11.9 mmol) in EtOAc (200 mL) furnished triketone **48** (0.90 g, 58 %) as a pale yellow oil after flash column chromatography (eluent 2:1 Et_2O:30-40 petrol);[29] ν_{max}/cm^{-1} (thin film) 1716 (C=O), 1694 (C=O); δ_H (400 MHz, $CDCl_3$) 1.24 (3H, s, C(2)CH_3), 1.84-1.98 (2H, m, C(5)H_2), 2.05 (2H, t, *J* 7.4, C(1')H_2), 2.11 (3H, s, C(4')H_3), 2.34 (2H, t, *J* 7.4, C(2')H_2), 2.59-2.76 (4H, m, C(4)H_2, C(6)H_2); δ_C (100 MHz, $CDCl_3$) 17.6 (*C*(5)H_2), 20.1 (C(2)*C*H_3), 29.5 (*C*(1')H_2), 30.0 (*C*(4')H_3), 37.7 (*C*(4)H_2, *C*(6)H_2), 38.3 (*C*(2')H_2), 64.3 (*C*(2)CH_3), 207.6 (*C*(3')O), 201.1 (*C*(1)O, *C*(3)O); *m/z* (GC ToF CI^+) 197 ($[M+H]^+$, 100 %); HRMS (GC ToF CI^+) $C_{12}H_{19}O_3$ ($[M+H]^+$) requires 197.1178 found 197.1185.

(*RS*)-8a-Methyl-3,4,8,8a-tetrahydronapthalene-(2*H*,7*H*)-1,6-dione 49



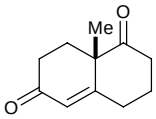
Following *General Procedure 2*, DL-proline **1** (26 mg, 0.23 mmol) was added to triketone **48** (150 mg, 0.76 mmol) in anhydrous DMF (2.0 mL). After 1 day the reaction was worked-up to furnish a 34:66 mixture of triketone **48** and enone **49** respectively (123 mg, 82 %) as a pale brown oil. Following *General Procedure 2*, the 34:66 mixture of **48** and **49** (123 mg, 0.63 mmol) and *p*-TsOH (12 mg, 0.06 mmol) in toluene (4.0 mL) furnished enone (*RS*)-**49** (70 mg, 63 %) as a pale brown oil;[30] ν_{max}/cm^{-1} (thin film) 1714 (C(1)=O), 1667 (C(6)=O), 1620 (C=C); δ_H (400 MHz, $CDCl_3$) 1.43 (3H, s, CH_3), 1.69 (1H, app qt, *J* 13.4, 4.4, C(3)$H_A$$H_B$), 2.08-2.17 (3H, m, C(3)$H_A$$H_B$, C(8)*H*), 2.41-2.52 (4H, m, C(2)$H_A$$H_B$, C(4)$H_A$$H_B$, C(7)$H_2$), 2.65-2.76 (2H, m, C(2)$H_A$$H_B$, C(4)$H_A$$H_B$), 5.83 (1H, s, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 22.9 (*C*(3)H_2), 23.3 (C(8a)*C*H_3), 29.6 (*C*(8)H_2), 31.7 (*C*(4)H_2), 33.6 (*C*(7)H_2), 37.6 (*C*(2)H_2), 50.6 (*C*(8a)CH_3), 125.8 (*C*(5)H), 165.8 (*C*(4a)), 198.3 (*C*(6)O), 211.0 (*C*(1)O); *m/z* (GC ToF CI^+) 179 ($[M+H]^+$, 100 %); HRMS (GC ToF CI^+) $C_{11}H_{15}O_2$ ($[M+H]^+$) requires 179.1072 found 179.1064.

---

[29] Triketone **48** has previously been reported but not fully characterized in P. Buchschacher and A. Fuerst, *Organic Syntheses*, 1985, **63**, 37.

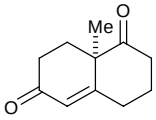
[30] Enone **49** has previously been reported but not fully characterized in E. Wada, J. Funakoshi and S. Kanemasa, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 2456.

(*S*)-8a-Methyl-3,4,8,8a-tetrahydronapthalene-(2*H*,7*H*)-1,6-dione 49



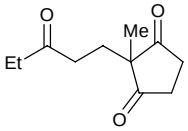
Following *General Procedure 2*, L-proline **1** (26 mg, 0.23 mmol) was added to triketone **48** (150 mg, 0.76 mmol) in anhydrous DMF (2.0 mL). After 6 days the reaction was worked-up to furnish enone (*S*)-**49** in 72 % e.e.[31] (98 mg, 72 %) as a pale brown oil; $[\alpha]_D^{23}$ +54.1 (*c* 1.0 in EtOH) {lit.,[32] *ent.* $[\alpha]_D^{25}$ –130 (*c* 0.7, EtOH)}.

(*R*)-8a-Methyl-3,4,8,8a-tetrahydronapthalene-(2*H*,7*H*)-1,6-dione 49



Following *General Procedure 2*, (1*R*,2*S*)-cispentacin **38** (20 mg, 0.15 mmol) was added to triketone **48** (100 mg, 0.51 mmol) in anhydrous DMF (2.0 mL). After 4.5 days a 1.0 mL aliquot was removed and worked-up to furnish enone (*R*)-**49** in 86 % e.e.[31] (34 mg, 75 %) as a pale brown oil; $[\alpha]_D^{23}$ –45.3 (*c* 0.75 in EtOH) {lit.,[32] $[\alpha]_D^{25}$ –130 (*c* 0.7, EtOH)}.

2-Methyl-2-(3'-oxopentyl)cyclopenta-1,3-dione 50



Following *General Procedure 1*, Et_3N (1.86 mL, 13.4 mmol), 2-methylcyclopenta-1,3-dione (1.00 g, 8.92 mmol) and ethyl vinyl ketone (1.33 mL, 13.4 mmol) in EtOAc (200 mL) furnished triketone **50** (1.57 g, 90 %) as a colourless oil after flash column chromatography (eluent 2:1 Et_2O:30-40 petrol);[33] ν_{max}/cm^{-1} (thin film) 1766 (C=O), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.00 (3H, t, *J* 7.3, C(5')H_3), 1.10 (3H, s, C(2)CH_3), 1.90 (2H, t, *J* 7.1, C(1')H_2), 2.38 (2H, q, *J* 7.3 C(4')H_2), 2.42 (2H, t, *J* 7.1, C(2')H_2), 2.70-2.90 (4H, m, C(4)H_2, C(5)H_2); δ_C (100 MHz, $CDCl_3$) 7.6 (*C*(5')H_3), 19.2 (C(2)*C*H_3), 27.9 (*C*(1')H_2), 34.7 (*C*(4)H_2, *C*(5)H_2), 36.0 (*C*(2')H_2), 36.1 (*C*(4')H_2), 55.2 (*C*(2)CH_3), 210.7 (*C*(3')O), 215.8 (*C*(1)O, *C*(3)O);

---

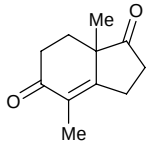
[31] The e.e. of enone **49** was determined using chiral GC analysis; ThermoQuest TRACE GC, fitted with a Cydex-β column, 110 ºC isotherm, 300 min and comparison with an authentic racemic sample, (*R*)-**49** t_R = 260.8 min, (*S*)-**49** t_R = 277.5 min.

[32] V. Prelog and W. Acklin, *Helv. Chim. Acta.*, 1956, **39**, 748.

[33] Triketone **50** has previously been reported but not fully characterized in R. C. Gupta and A. Nitya, *Indian J. Chem.*, 1975, **13**, 759.

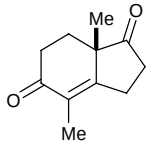
m/z (GC ToF CI$^+$) 197 ([M+H]$^+$, 100%); HRMS (GC ToF CI$^+$) $C_{12}H_{19}O_3$ ([M+H]$^+$) requires 197.1178 found 197.1186.

(*RS*)-4,7a-Dimethyl-2,3,7,7a-tetrahydro-(6*H*)-indene-1,5-dione 52



Following *General Procedure 2*, triketone **50** (150 mg, 0.76 mmol) and *p*-TsOH (15 mg, 0.08 mmol) in toluene (3.0 mL) furnished enone (*RS*)-**52** (120 mg, 88 %) as a pale brown oil;[34] ν_{max}/cm^{-1} (thin film) 1746 (C(1)=O), 1663 (C(5)=O), 1652 (C=C); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, s, C(7a)CH_3), 1.75 (3H, s, C(4)CH_3), 1.77-1.86 (1H, m, C(6)H_AH$_B$), 2.01-2.07 (1H, m, C(6)H_AH$_B$), 2.35-2.59 (3H, m, C(2)H_AH$_B$, C(7)H_2), 2.70-2.84 (2H, m, C(2)H$_A$$H_B$, C(3)H$_A$$H_B$), 2.84-2.95 (1H, m, C(3)H$_A$$H_B$); δ_C (100 MHz, $CDCl_3$) 10.7 (C(4)*C*H$_3$), 21.2 (C(7a)*C*H$_3$), 24.5 (*C*(3)H$_2$), 28.7 (*C*(6)H$_2$), 32.7 (*C*(7)H$_2$), 35.4 (*C*(2)H$_2$), 48.9 (*C*(7a)CH$_3$), 129.8 (*C*(4)CH$_3$), 162.6 (*C*(3a)), 198.0 (*C*(5)O), 217.7 (*C*(1)O); *m/z* (GC ToF CI$^+$) 179 ([M+H]$^+$, 100 %); HRMS (GC ToF CI$^+$) $C_{11}H_{15}O_2$ ([M+H]$^+$) requires 179.1072 found 179.1072.

(*S*)-4,7a-Dimethyl-2,3,7,7a-tetrahydro-(6*H*)-indene-1,5-dione 52

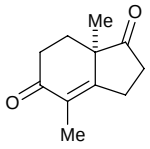


Following *General Procedure 2*, L-proline **1** (26 mg, 0.23 mmol) was added to triketone **50** (150 mg, 0.76 mmol) in anhydrous DMF (3.0 mL) at 60 °C. After 7 days the reaction was worked-up and purified via flash column chromatography (eluent Et_2O) to afford ketol **51** (122 mg, 81 %) as a pale orange solid;[35] mp 126-128 ºC (lit.,[36] mp 160-161 ºC); $[\alpha]_D^{21}$ +28.8 (*c* 0.85 in $CHCl_3$) {lit.,[36] $[\alpha]_D^{25}$ +34.6 (*c* 1.0, $CHCl_3$)}; ν_{max}/cm^{-1} (KBr disc) 3437 (O–H), 1738 (C=O), 1699 (C=O); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.7, C(4)CH_3), 1.30 (3H, s, C(7a)CH_3), 1.50-1.65 (2H, m, C(7)H_2), 1.65-1.74 (1H, m, C(3)H_AH$_B$), 1.89-2.02 (1H, m, C(3)H$_A$$H_B$), 2.28-2.36 (1H, m, C(6)H_AH$_B$), 2.38-2.44 (2H, m, C(2)H_2), 2.46-2.56 (1H, m, C(6)H$_A$$H_B$), 2.69-2.76 (1H, q, *J* 6.7, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 6.7 (C(4)*C*H$_3$), 12.5 (C(7a)*C*H$_3$), 28.4

[34] Enone **52** has previously been reported but not fully characterized in A. Balog, S. J. Geib and D. P. Curran, *J. Org. Chem.*, 1995, **60**, 345.
[35] Ketol **51** has previously been reported but not fully characterized in M. Medarde, E. Caballero, C. P. Melero, F. Tomé and A. S. Feliciano, *Tetrahedron: Asymmetry*, 1997, **8**. 2075; Z. G. Hajos and D. R. Parrish, 1976, *US.Pat.* **3.975442**.
[36] Z. G. Hajos and D. R. Parrish, 1976, *US.Pat.* **3.975442**.

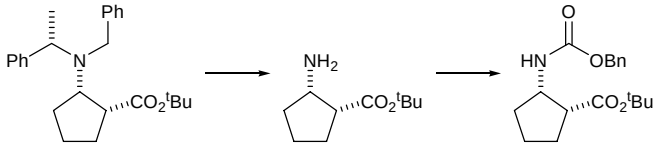
(C(3)H_2), 29.9 (C(7)H_2), 32.7 (C(2)H_2), 37.0 (C(6)H_2), 51.0 (C(4)CH_3), 53.5 (C(7a)CH_3), 84.6 (C(3a)), 209.2 (C(5)O), 218.7 (C(1)O); *m/z* (ESI$^-$) 195 ([M–H]$^-$, 50 %); HRMS (ESI$^-$) $C_{11}H_{15}O_3$ ([M–H]$^-$) requires 195.1021; found 195.1022. Subsequently, following *General Procedure 2*, ketol **51** (20 mg, 0.10 mmol) and *p*-TsOH (2 mg, 0.01 mmol) in toluene (1.0 mL) furnished enone (*S*)-**52** in 71 % e.e.[37] (17 mg, 94 %) as a pale brown oil; $[\alpha]_D^{21}$ +75.0 (*c* 0.7 in $CHCl_3$) {lit.,[38] *ent*. $[\alpha]_D^{21}$ –328 (*c* 1.1 in $CHCl_3$)}.

(*R*)-4,7a-Dimethyl-2,3,7,7a-tetrahydro-(6*H*)-indene-1,5-dione 52



Following *General Procedure 2*, (1*R*,2*S*)-cispentacin **38** (20 mg, 0.15 mmol) was added to triketone **50** (100 mg, 0.51 mmol) in anhydrous DMF (1.5 mL) at 60 °C. After 9 days a 0.9 mL aliquot was removed and worked-up to furnish ketol **51** (51 mg, 76 %) as a pale yellow solid; this material (50 mg, 0.26 mmol) was immediately dehydrated according to *General Procedure 2*, with *p*-TsOH (5 mg, 0.03 mmol) in toluene (2.0 mL) to furnish enone (*R*)-**52** in 27 % e.e.,[37] (38 mg, 83 %) as a pale brown oil; $[\alpha]_D^{23}$ –24.8 (*c* 0.85 in $CHCl_3$) {lit.,[38] $[\alpha]_D^{21}$ –328 (*c* 1.1, $CHCl_3$)}.

***tert*-Butyl (1*R*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxylate 55**



$Pd(OH)_2$/C (7.75 g, 25 % w/w) was added to a stirred, degassed solution of β-amino ester *tert*-butyl (1*R*,2*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclopentane-1-carboxylate (31.0 g, 81.7 mmol) and AcOH (3 mL) in MeOH (150 mL). The resulting suspension was vigorously stirred under an atmosphere of hydrogen (5 atm) for 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was then re-dissolved in DCM and the resultant solution was washed with sat. aq. $NaHCO_3$ solution then dried over $MgSO_4$, filtered and concentrated *in*

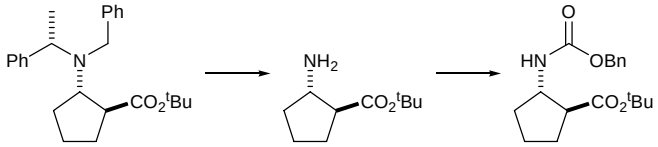
[37] The e.e. of enone **52** was determined using chiral GC analysis; ThermoQuest TRACE GC, fitted with a Cydex-β column, 120 ºC isotherm, 140 min and comparison with an authentic racemic sample, (*R*)-**52** t_R = 111.9 min, (*S*)-**52** t_R = 118.5 min.

[38] H. Hioki, T. Hashimoto and M. Kodama, *Tetrahedon: Asymmetry*, 2000, **11**, 829.

vacuo to afford *tert*-butyl (1*R*,2*S*)-2-aminocyclopentane-1-carboxylate (14.01 g, 93 %) as a colourless oil; $[\alpha]_D^{22}$ –5.1 (*c* 1.0 in $CHCl_3$) {lit.,[39] $[\alpha]_D^{24}$–5.6 (*c* 0.6 in $CHCl_3$)}.

Et_3N (0.26 mL, 1.840 mmol) and CbzCl 0.26 mL, 1.84 mmol) were added successively to a solution of *tert*-butyl (1*R*,2*S*)-2-aminocyclopentane-1-carboxylate (310 mg, 1.67 mmol) in anhydrous THF (3.0 mL) at 0 ºC. The resultant mixture was allowed to warm to rt then stirred for 16 h. The reaction mixture was then washed with brine (5 mL) and the aqueous layer was extracted with two portions of DCM (2 × 5 mL). The combined organic extracts were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue via flash column chromatography (eluent 4:1 30-40 petrol:Et_2O) furnished (1*R*,2*S*)-**55** (400 mg, 75 %) as a colourless oil, which slowly crystallized upon standing to a white solid; (Found: C, 67.7; H, 7.9; N, 4.4. $C_{14}H_{16}N_2O_2$ requires C, 67.7; H, 4.4; N, 4.4 %); mp 42-43 °C; $[\alpha]_D^{20}$ –41.5 (*c* 1.1 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3336 (N–H), 1724 (C=O carbamate, C=O ester); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, m, C(CH_3)$_3$), 1.54-1.71 (2H, m, C(3)H_2), 1.74-2.02 (4H, m, C(4)H_2, C(5)H_2), 2.90 (1H, app q, *J* 7.4 C(1)*H*), 4.23-4.31 (1H, m, C(2)*H*), 5.10 (2H, s, CH_2Ph), 5.24-5.34 (1H, br m, N*H*) 7.28-7.42 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.2 (*C*(4)H_2), 27.7 (*C*(5)H_2), 28.0 (C(*C*H_3)$_3$), 32.4 (*C*(3)H_2), 47.6 (*C*(1)H), 54.2 (*C*(2)H), 66.6 (*C*H_2Ph), 80.8 (*C*(CH_3)$_3$), 128.0, 128.1, 128.5 (*o,m,p-Ph*), 136.6 (*i-Ph*), 155.8 (*C*ONH), 173.6 (*C*O^{t}Bu); *m/z* (ESI^+) 378 ([M+MeCN+NH_4]$^+$, 100 %); HRMS (ESI^+) $C_{18}H_{26}N_1O_4$ ([M+H]$^+$) requires 320.1862; found 320.1866.

tert-Butyl (1*S*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxylate 56



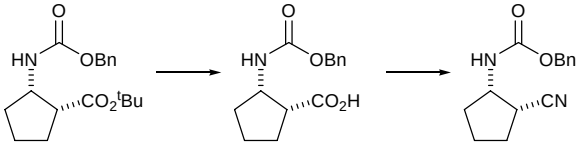
$Pd(OH)_2$/C (7.75 g, 25 % w/w) was added to a stirred, degassed solution of *tert*-butyl (1*S*,2*S*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclopentane-1-carboxylate (20.6 g, 54.3 mmol) in MeOH (100 mL). The resulting suspension was vigorously stirred under an atmosphere of hydrogen (5 atm.) 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to afford *tert*-butyl (1*S*,2*S*)-2-aminocyclopentane-1-carboxylate (7.00 g, 71 %) as a colourless oil; $[\alpha]_D^{22}$ +34.7 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (1H, m, C(5)H_AH_B), 1.29 (2H, s, NH_2), 1.33 (9H, s, C(CH_3)$_3$), 1.49-1.60 (2H, m, C(4)H_2), 1.64-1.75 (1H, m, C(3)H_AH_B), 1.79-1.89 (2H, m, C(3)H_AH_B, C(5)H_AH_B), 2.19 (1H, app q, *J* 8.3, C(2)*H*), 3.26 (1H, app q, *J*

[39] S. G. Davies, O. Ichihara, I. Lenoir, I. A. S. Walters, *J. Chem. Soc., Perkin Trans. 1*, 1994, **11**, 1411.

7.3, C(1)*H*); δ_C (100 MHz, $CDCl_3$) 22.4 (*C*(4)H_2), 27.9 (*C*(5)H_2), 28.0 (C(*C*H_3)$_3$), 35.1 (*C*(3)H_2), 54.5 (*C*(1)H), 57.0 (*C*(2)H), 79.9 (*C*(CH_3)$_3$), 174.5 (*C*O_2^{t}Bu); *m/z* (GC ToF CI^+) 186 ($[M+H]^+$, 100 %); HRMS (GC ToF CI^+) $C_{10}H_{20}NO_2$ ($[M+H]^+$) requires 186.1494; found 186.1489

Et_3N (5.80 mL, 41.6 mmol) and CbzCl (5.93 mL, 41.5 mmol) were added successively to a solution of *tert*-butyl (1*S*,2*S*)-2-aminocyclopentane-1-carboxylate (7.00 g, 37.8 mmol) in anhydrous THF (100 mL) at 0 ºC. The resultant mixture was allowed to warm to rt and then stirred for 16 h. The reaction mixture was then washed with brine (150 mL) and the aqueous layer was extracted with two portions of DCM (2 × 100 mL). The combined organic extracts were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue via flash column chromatography (eluent 9:1 pentane:Et_2O) furnished (1*S*,2*S*)-**56** (10.2 g, 85 %) as a colourless oil; $[\alpha]_D^{24}$ –44.5 (*c* 0.7 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3338 (N–H), 1725 (C=O carbamate, C=O ester); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, m, C(CH_3)$_3$), 1.39-1.51 (1H, m, C(3)H_AH$_B$), 1.67-1.74 (2H, m, C(4)H_2), 1.83-1.99 (2H, m, C(5)H_2), 2.10-2.18 (1H, m, C(3)H$_A$$H_B$), 2.90 (1H, app q, *J* 8.1 C(1)*H*), 4.13-4.20 (1H, m, C(2)*H*), 4.82 (1H, app br s, N*H*), 5.10 (2H, s, CH_2Ph), 7.27-7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.8 (*C*(4)H_2), 28.0 (*C*(5)H_2), 28.0 (C(*C*H_3)$_3$), 33.2 (*C*(3)H_2), 51.7 (*C*(1)H), 56.2 (*C*(2)H), 65.4 (*C*H_2Ph), 80.6 (*C*(CH_3)$_3$), 128.1, 128.5, 128.6 (*o*,*m*,*p*-*Ph*), 136.6 (*i*-*Ph*), 155.6 (*C*ONH), 173.6 (*C*O^{t}Bu); *m/z* (ESI^+) 342 ($[M+Na]^+$, 100 %); HRMS (ESI^+) $C_{18}H_{25}N_1O_4Na$ ($[M+Na]^+$) requires 342.1681; found 342.1677.

(1*R*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carbonitrile 57



TFA (15 mL) was added to a solution of ester (1*R*,2*S*)-**55** (12.9 g, 40.4 mmol) in DCM (60 mL) at 0 ºC. The resultant mixture was then allowed to warm to rt and was stirred for 4 h. After this time all volatiles were removed *in vacuo*. Purification of the residue via flash column chromatography (eluent 1:1 30-40 petrol:Et_2O) furnished (1*R*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxylic acid (10.6 g, quant) as a colourless oil; $[\alpha]_D^{22}$ –44.7 (*c* 1.1 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2963 (N–H), 1716 (C=O carbamate, C=O acid); δ_H (400 MHz, MeOD) 1.54-1.75 (2H, m, C(3)H_AH$_B$, C(4)H_AH$_B$), 1.80-2.06 (4H, m, C(3)H$_A$$H_B$, C(4)H$_A$$H_B$, C(5)$H_2$), 2.99 (1H, app q, *J* 7.4 C(1)*H*), 4.25 (1H, app q, *J* 7.1, C(2)*H*), 5.07 (2H, s, CH_2Ph), 7.26-7.43 (5H, m, *Ph*); δ_C (100 MHz, MeOD) 22.1 (*C*(4)H_2), 27.2 (*C*(5)H_2), 31.6 (*C*(3)H_2), 47.6 (*C*(1)H), 54.7 (*C*(2)H), 66.4 (*C*H_2Ph), 127.7, 127.9, 128.5 (*o*,*m*,*p*-*Ph*), 137.4 (*i*-*Ph*), 157.3

(*C*ONH), 176.3 (*C*O_2H); *m/z* (ESI$^+$) 286 ([M+Na]$^+$, 100 %); HRMS (ESI$^+$) $C_{14}H_{17}N_1O_4Na$ ([M+Na]$^+$) requires 286.1053; found 286.1005.

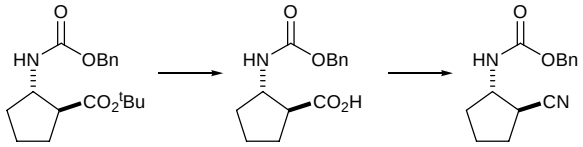
Pyridine (0.03 mL, 0.35 mmol) was slowly added to a solution of (1*R*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxylic acid (150 mg, 0.57 mmol), Boc_2O (162 mg, 0.741 mmol)and NH_4HCO_3 (57 mg, 0.70 mmol) in MeCN (2.0 mL) at rt.[40] The reaction mixture was then left to stir for 16 h at rt, after this time H_2O (0.5 mL) was added and the volatiles were removed *in vacuo* prior to filtration. The residue was then washed with H_2O (10 mL) and hexane (10 mL) then re-dissolved in DCM (20 mL). The resultant organic solution was dried over $MgSO_4$, filtered and concentrated *in vacuo* to furnish (1*R*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxamide (120 mg, 80 %) as a white solid; (Found: C, 64.4; H, 6.7; N, 10.3. $C_{14}H_{16}N_2O_2$ requires C, 64.1; H, 6.9; N, 10.7 %); mp 171-172 ºC; $[\alpha]_D^{23}$ –13.5 (*c* 1.0 in $CHCl_3$; ν_{max}/cm^{-1} (KBr disc) 3336 (N–H), 1668 (C=O carbamate), 1633 (C=O amide); δ_H (500 MHz, MeOD) 1.55-1.64 (1H, m, C(3)H_AH_B), 1.71-1.78 (1H, m, C(4)H_AH_B), 1.82-2.02 (4H, m, C(3)H_AH_B, C(4)H_AH_B, C(5)H_2), 2.91-2.96 (1H, m, C(1)*H*), 4.16-4.22 (1H, m, C(2)*H*), 5.08 (2H, s, CH_2Ph), 7.28-7.37 (5H, m, *Ph*); δ_C (125 MHz, MeOD) 22.1 (*C*(4)H_2), 27.4 (*C*(5)H_2), 32.0 (*C*(3)H_2), 47.6 (*C*(1)H), 54.4 (*C*(2)H), 66.0 (*C*H_2Ph), 127.3, 127.5, 128.0 (*o,m,p-Ph*), 136.9 (*i-Ph*), 156.9 (*C*O_2CH_2Ph), 177.3 (*C*ONH_2); *m/z* (ESI$^+$) 285 ([M+Na]$^+$, 100 %); HRMS (ESI$^+$) $C_{14}H_{18}N_2O_3Na$ ([M+Na]$^+$) requires 285.1215; found 285.1207.

Cyanuric chloride (3.27 g, 17.7 mmol) was added to a flask containing a solution of (1*R*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxamide (7.15 g, 27.3 mmol) in DMF (140 mL) at 0 ºC.[40] The reaction mixture was then allowed to warm to rt and stirred for 16 h. H_2O (500 mL) was then added and the resultant mixture was extracted with three portions of EtOAc (3 × 400 mL). The combined organic extracts were washed with five portions of H_2O (5 × 500 mL) then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then dissolved in a 1:2 mixture of EtOAc and hexane and passed through a short plug of silica (eluent 1:2 EtOAc:hexane). The resultant solution was concentrated *in vacuo* to furnish nitrile (1*R*,2*S*)-**57** (6.90 g, quant) as a colourless oil; (Found: C, 68.65; H, 6.7; N, 11.5. $C_{14}H_{16}N_2O_2$ requires C, 68.8; H, 6.6; N, 11.5 %); $[\alpha]_D^{22}$ –91.0 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3333 (N–H), 2240 (C≡N), 1698 (C=O); δ_H (500 MHz, MeOD) 1.64-1.72 (2H, m, C(3)H_AH_B, C(4)H_AH_B), 1.85-2.17 (4H, m, C(3)H_AH_B, C(4)H_AH_B, C(5)H_2), 3.23 (1H, app q, *J* 6.9, C(1)*H*), 4.18 (1H, app q, *J* 7.4, C(2)*H*), 5.13 (2H, s, CH_2Ph), 7.29-7.39 (5H, m, *Ph*); δ_C (125 MHz, MeOD) 21.9 (*C*(4)H_2), 28.8 (*C*(5)H_2),

[40] Z. P. Demko, K. B. Sharpless, *Org. Lett.*, 2002, **4**, 2525.

30.0 (*C*(3)H_2), 34.4 (*C*(1)H), 53.6 (*C*(2)H), 66.2 (*C*H_2Ph), 120.0 (*C*N), 127.3, 127.6, 128.1 (*o,m,p-Ph*), 136.9 (*i-Ph*), 171.6 (NH*C*O); *m/z* (CI^+) 245 ($[M+H]^+$, 100 %); HRMS (CI^+) $C_{14}H_{17}N_2O_2$ ($[M+H]^+$) requires 245.129003; found 245.129085.

(1*S*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carbonitrile 58



TFA (12 mL) was added to a solution ester (1*S*,2*S*)-**56** (9.30 g, 29.1 mmol) in DCM (50 mL) at 0 ºC. The resultant mixture was then allowed to warm to rt and was stirred for 4 h. After this time all volatiles were removed *in vacuo*. Purification of the residue via recrystalization (DCM/pentane) furnished (1*S*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxylic acid (7.66 g, quant) as a white solid; mp 100-101 °C ($CHCl_3$/*n*-heptane); $[\alpha]_D^{23}$ +23.5 (*c* 1.3 in $CHCl_3$); ν_{max}/cm^{-1} (KBr disc) 3320 (N–H), 1710 (C=O carbamate, C=O acid); δ_H (500 MHz, MeOD) 1.52-1.59 (1H, m, C(3)H_AH_B),1.65-1.77 (2H, m, C(4)H_2), 1.78-1.91 (1H, m, C(5)H_AH_B), 1.96-2.07 (2H, m, C(3)H_AH_B, C(5)H_AH_B), 2.64-2.72 (1H, m, C(1)*H*), 4.19-4.26 (1H, m, C(2)*H*), 5.06 (2H, s, CH_2Ph), 7.26-7.37 (5H, m, *Ph*); δ_C (100 MHz, MeOD) 24.3 (*C*(4)H_2), 30.0 (*C*(5)H_2), 33.9 (*C*(3)H_2), 51.6 (*C*(1)H), 57.4 (*C*(2)H), 67.5 (*C*H_2Ph), 128.9, 129.0, 129.6 (*o,m,p-Ph*), 138.4 (*i-Ph*), 158.4 (*C*ONH), 178.7 (*C*O_2H); *m/z* (ESI^-) 262 ($[M–H]^-$, 85 %); HRMS (ESI^-) $C_{14}H_{16}N_1O_4$ ($[M–H]^-$) requires 262.1079; found 262.1078.

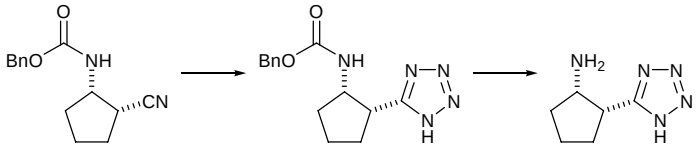
Pyridine (13 μL, 0.17 mmol) was slowly added to a solution of (1*S*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxylic acid (70 mg, 0.27 mmol), Boc_2O (76 mg, 0.35 mmol) and NH_4HCO_3 (27 mg, 0.33 mmol) in MeCN (1.0 mL) at rt.[41] The reaction mixture was then left to stir for 16 h at rt, after this time H_2O (0.5 mL) was added and the volatiles were removed *in vacuo* prior to filtration. The residue was washed with H_2O (10 mL) and hexane (10 mL) then re-dissolved in MeOH (20 mL), filtered and concentrated *in vacuo* to furnish (1*S*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxamide (57 mg, 82 %) as a white solid; mp 193-197 ºC; $[\alpha]_D^{24}$ +30.8 (*c* 0.25 in $CHCl_3$); ν_{max}/cm^{-1} (KBr disc) 3415, 3319 (N–H), 1662 (C=O carbamate, C=O amide); δ_H (500 MHz, DMSO-d_6) 1.39-1.45 (1H, m, C(3)H_AH_B), 1.52-1.67 (3H, m, C(4)H_2, C(5)H_AH_B), 1.81-1.92 (2H, m, C(3)H_AH_B, C(5)H_AH_B), 2.46-2.51 (1H, m, C(1)*H*), 3.31 (1H, app obsc s CON*H*) 3.94-4.01 (1H, m, C(2)*H*), 5.00 (2H, s, CH_2Ph), 6.77, 7.19 (2H, 2 × app br s, CONH_2) 7.31-7.39 (5H, m, *Ph*);

[41] Z. P. Demko, K. B. Sharpless, *Org. Lett.*, 2002, **4**, 2525.

δ_C (125 MHz, DMSO-d_6) 23.2 (*C*(4)H_2), 28.9 (*C*(5)H_2), 32.9 (*C*(3)H_2), 50.2 (*C*(1)H), 55.4 (*C*(2)H), 65.2 (*C*H_2Ph), 127.8, 127.9, 128.4 (*o,m,p-Ph*), 137.1 (*i-Ph*), 155.5 (*C*O_2CH_2Ph), 175.7 (*C*ONH_2); *m/z* (ESI^+) 285 ($[M+Na]^+$, 100 %); HRMS (ESI^+) $C_{14}H_{19}N_2O_3$ ($[M+H]^+$) requires 263.1396; found 263.1390.

Cyanuric chloride (2.92 g, 15.8 mmol) was added to a solution of (1*S*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxamide (6.38 g, 24.3 mmol) in DMF (120 mL) at 0 ºC. The reaction mixture was then allowed to warm to rt and stirred for 16 h. H_2O (500 mL) was then added and the resultant mixture was extracted with three portions of EtOAc (3 × 400 mL). The combined organic extracts were washed with five portions of H_2O (5 × 500 mL) then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then dissolved in a 1:2 mixture of EtOAc and hexane and passed through a short plug of silica (eluent 1:2 EtOAc:hexane). The resultant solution was concentrated *in vacuo* to furnish nitrile (1*S*,2*S*)-**58** (6.00 g, quant) as a pale yellow oil that slowly solidified upon standing to a pale yellow solid; (Found: C, 68.3; H, 6.8; N, 11.2. $C_{14}H_{16}N_2O_2$ requires C, 68.8; H, 6.6; N, 11.5 %); mp 53-56 ºC; $[\alpha]_D^{22}$ +71.0 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} (KBr disc) 3327 (N–H), 2239 (C≡N), 1688 (C=O); δ_H (500 MHz, MeOD) 1.53-1.63 (1H, m, C(3)H_AH_B), 1.75-1.85 (2H, m, C(4)H_2), 1.85-1.93 (1H, m, C(5)H_AH_B), 2.06-2.20 (2H, C(3)H_AH_B, C(5)H_AH_B), 2.80-2.85 (1H, m, C(1)*H*), 4.16-4.21 (1H, m, C(2)*H*), 5.11 (2H, s, CH_2Ph), 7.29-7.43 (5H, m, *Ph*); δ_C (125 MHz, MeOD) 23.5 (*C*(4)H_2), 30.2 (*C*(5)H_2), 32.4 (*C*(3)H_2), 36.0 (*C*(1)H), 58.2 (*C*(2)H), 67.6 (*C*H_2Ph), 122.9 (*C*N), 128.9, 129.1, 129.5 (*o,m,p-Ph*), 138.2 (*i-Ph*), 158.2 (NH*C*O); *m/z* (CI^+) 267 ($[M+Na]^+$, 100 %); HRMS (CI^+) $C_{14}H_{17}N_2O_2$ ($[M+H]^+$) requires 245.1290; found 245.1282.

(1'*R*,2'*S*)-5-(2'-aminocyclopentan-1'-yl)tetrazole 59

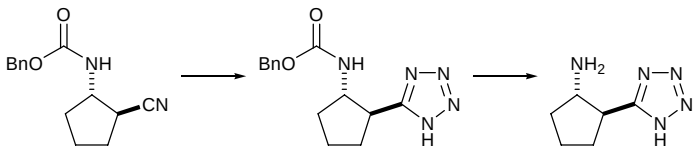


Nitrile (1*R*,2*S*)-**57** (1.02 g, 4.15 mmol), NaN_3 (2.70 g, 41.5 mmol) and $ZnBr_2$ (1.40 g, 6.22 mmol) in propan-2-ol (6 mL) and H_2O (12 mL) was heated at reflux for 5 days. After this time 3.0 M aq. HCl solution (6 mL) and EtOAc (6 mL) were added to the mixture and stirring was continued until all solid residues had dissolved. The organic layer was then separated and the aqueous layer was extracted with three portions of EtOAc (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to furnish a 89:11 mixture of the desired tetrazole and hydrolysis product respectively. The residue was partitioned between 1.0 M aq. NH_4OH (15 mL) and $CHCl_3$ (15 mL). The

aqueous layer was then washed with $CHCl_3$ (3 × 15 mL) and concentrated *in vacuo* to afford (1'*R*,2'*S*)-5-{2'-[*N*-(benzyloxycarbonyl)amino]cyclopentan-1'-yl}tetrazole (970 mg, 81 %) as a white solid; mp 220 ºC (dec.); $[\alpha]_D^{22}$ +5.4 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} (KBr disc) 3441 (N–H), 1631 (C=N, C=O), 1524 (N=N); δ_H (500 MHz, MeOD) 1.64-1.73 (1H, m, C(4')H_AH_B), 1.80-1.86 (1H, m, C(3')H_AH_B), 1.90-1.98 (1H, m, C(4')H_AH_B), 2.03-2.18 (3H, m, C(3')H_AH_B, C(5')H_2), 3.79-3.84 (1H, m, C(1')*H*), 4.34-4.38 (1H, m, C(2')*H*), 4.86 (2H, obsc s, CH_2Ph), 7.21-7.37 (5H, m, *Ph*); δ_C (125 MHz, MeOD) 21.9 (*C*(4')H_2), 29.4 (*C*(5')H_2), 32.1 (*C*(3')H_2), 39.4 (*C*(1')H), 54.9 (*C*(2')H), 66.0 (*C*H_2Ph), 127.3, 127.5, 128.1 (*o*,*m*,*p*-*Ph*), 136.7 (*i*-*Ph*), 156.6 (NH*C*O), 162.2 (*C*(5)N); *m/z* (ESI^-) 286 ($[M–H]^-$ 100 %); HRMS (ESI^-) $C_{14}H_{16}N_5O_2$ ($[M–H]^-$) requires 245.1304; found 245.1308.

Pearlman's catalyst (260 mg, 25 % w/w) was added to a stirred solution of (1'*R*,2'*S*)-5-{2'-[*N*-(benzyloxycarbonyl)amino]cyclopentan-1'-yl}tetrazole (1.05 g, 3.65 mmol) in degassed MeOH (20 mL). The resulting suspension was stirred under a H_2 atmosphere (5 atm) for 40 h, after which time the reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to furnish *cis*-β-amino tetrazole (1'*R*,2'*S*)-**59** (552 mg, quant) as a white solid; mp 250-252 ºC; $[\alpha]_D^{23}$ –1.2 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} (KBr disc) 1387 (N=N), 1473 (N=N), 1618 (C=N) 1639 (C=N), 3418 (N–H); δ_H (500 MHz, D_2O) [(1'*R*,2'*S*)-**59** exists as a mixture of 1*H*- and 2*H*-tautomers in solution, only data for the major tautomer is given] 1.42-1.51 (1H, m, C(3')H_AH_B), 1.55-1.67 (1H, m, C(4')H_AH_B), 1.74-1.83 (1H, m, C(4')H_AH_B), 1.88-2.03 (3H, m, C(3')H_AH_B, C(5')H_2), 3.31 (1H, app q, *J* 7.7, C(1')*H*), 3.45-3.52 (1H, m, C(2')*H*); δ_C (125 MHz, D_2O); 21.4 (*C*(4')H_2), 27.5 (*C*(5')H_2), 31.7 (*C*(3')H_2), 38.4 (*C*(2')H), 40.7 (*C*(1')H), 163.0 (*C*(5)N); *m/z* (ESI^+) 217 ($[M+MeCN+Na]^+$ 100 %); HRMS (ESI^+) $C_6H_{12}N_5$ ($[M+H]^+$) requires 154.1093; found 154.1089.

(1'*S*,2'*S*)-5-(2'-aminocyclopentan-1'-yl)tetrazole 60

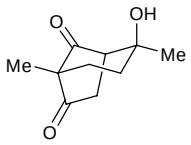


Nitrile (1*S*,2*S*)-**58** (954 mg, 3.91 mmol), NaN_3 (2.53 g, 38.9 mmol) and $ZnBr_2$ (1.32 g, 5.86 mmol) in *i*-PrOH (6mL) and H_2O (12 mL) was heated at reflux for 3 days. After this time 3.0 M aq. HCl solution (1 mL) and EtOAc (6 mL) were added to the mixture and stirring was continued until all solid residues had dissolved. H_2O (10 mL) was added and the aqueous layer was then extracted with three portions of EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in*

vacuo to furnish a 98:2 mixture of the desired tetrazole and hydrolysis product respectively. The residue was partitioned between 1.0 M aq. NH_4OH (15 mL) and $CHCl_3$ (15 mL). The aqueous layer was then washed with $CHCl_3$ (3 × 15 mL) and concentrated *in vacuo* to afford (1'*S*,2'*S*)-5-{2'-[*N*-(benzyloxycarbonyl)amino]cyclopentan-1'-yl}tetrazole (694 mg, 62 %) as a white solid; mp 230 ºC (dec.); $[\alpha]_D^{22}$ +43.4 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} (KBr disc) 3392 (N–H), 1699 (C=N, C=O), 1553 (N=N); δ_H (500 MHz, MeOD) 1.61-1.68 (1H, m, C(3')H_AH_B), 1.81-1.87 (2H, m, C(4')H_2), 1.92-2.00 (1H, m, C(5')H_AH_B), 2.13-2.23 (2H, m, C(3')H_AH_B, C(5')H_AH_B), 3.31-3.36 (1H, m, C(1')*H*), 4.25-4.29 (1H, m, C(2')*H*), 5.00 (2H, s, CH_2Ph), 7.24-7.39 (5H, m, *Ph*); δ_C (125 MHz, MeOD) 23.7 (*C*(4')H_2), 32.3 (*C*(5')H_2), 33.6 (*C*(3')H_2), 43.6 (*C*(1')H), 59.5 (*C*(2')H), 67.3 (*C*H_2Ph), 128.7, 128.9, 129.5 (*o,m,p-Ph*), 138.4 (*i-Ph*), 158.3 (NH*C*O), 165.0 (*C*(5)N); *m/z* (ESI^+) 310 ($[M+Na]^+$ 100 %); HRMS (ESI^+) $C_{14}H_{17}N_5O_2Na$ ($[M+H]^+$) requires 310.1274; found 310.1263.

$Pd(OH)_2$/C (170 mg, 25 % w/w) was added to a stirred solution of (1'*S*,2'*S*)-5-{2'-[*N*-(benzyloxycarbonyl)amino]cyclopentan-1'-yl}tetrazole (694 mg, 2.42 mmol) in degassed MeOH (20 mL). The resulting suspension was stirred under a H_2 atmosphere (1 atm) for 16 h, after which time the reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to furnish *trans*-β-amino tetrazole (1'*S*,2'*S*)-**60** (370 mg, quant) as a white solid; mp 194 ºC (dec); $[\alpha]_D^{23}$ +47.2 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} (KBr disc) 3407 (N–H), 1650 (C=N), 1583 (C=N), 1412 (N=N), 1395 (N=N); δ_H (500 MHz, MeOD) [(1'*S*,2'*S*)-**60** exists as a mixture of *H*-1 and *H*-2 tautomers in solution, only data for the major tautomer is given] 1.55-1.63 (1H, m, C(3')H_AH_B), 1.80-1.92 (2H, m, C(4')H_2), 1.92-1.99 (1H, m, C(5')H_AH_B), 2.11-2.18 (1H, m, C(3')H_AH_B), 2.20-2.26 (1H, m, C(5')H_AH_B), 3.05-3.11 (1H, m, C(1')*H*), 3.42-3.51 (1H, m, C(2')*H*); δ_C (125 MHz, MeOD) 23.4 (*C*(4')H_2), 32.3 (*C*(3')H_2), 33.5 (*C*(5')H_2), 46.3 (*C*(1')H), 59.8 (*C*(2')H), 165.2 (*C*(5)N); *m/z* (ESI^+) 154 ($[M+H]^+$ 100 %); HRMS (ESI^+) $C_6H_{12}N_5$ ($[M+H]^+$) requires 154.1093; found 154.1098.

(1*RS*,4*RS*,5*SR*)-1,5-Dimethyl-5-hydroxy-bicyclo[3.2.1]octan-2,8-dione 61



Following *General Procedure 2*, *cis*-β-amino tetrazole (1'*R*,2'*S*)-**59** (38 mg, 0.25 mmol) was added to triketone **9** (150 mg, 0.82 mmol) in anhydrous DMF (2.0 mL). After 24 h a 0.5 mL aliquot was removed and worked-up. Purification of the residue via flash column chromatography (eluent 1:2 30-40 petrol:

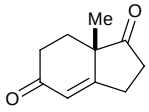
Et_2O) afforded racemic[42] **61** (25 mg, 67 %) as a white crystalline solid;[43] mp 140-146 ºC (lit.,[43] mp 160-161 ºC); ν_{max}/cm^{-1} (KBr disc) 3472 (O–H), 1770, 1728 (2 × C=O); δ_H (500 MHz, $CDCl_3$) 1.13 (3H, s, C(1)CH_3), 1.46 (3H, s, C(5)CH_3), 1.72-1.84 (2H, m, C(6)H_2), 1.86-1.94 (1H, m, C(7)H_AH$_B$), 2.09 (1H, br s, O*H*), 2.15-2.22 (1H, m, C(7)H$_A$$H_B$), 2.56-2.72 (2H, m, C(3)H_2), 2.83-2.86 (1H, m, C(4)*H*); δ_C (125 MHz, $CDCl_3$) 11.8 (C(1)*C*H$_3$), 28.4 (C(5)*C*H$_3$), 32.2 (*C*(6)H$_2$), 38.4 (*C*(7)H$_2$), 42.6 (*C*(3)H$_2$), 57.4 (*C*(4)H), 58.6 (*C*(1)CH$_3$), 80.5 (*C*(5)CH$_3$), 211.0, 213.8 (*C*(2)O, *C*(8)O); *m/z* (ESI$^-$) 181 ([M–H]$^-$, 100 %); HRMS (ESI$^-$) $C_{10}H_{13}O_3$ ([M–H]$^-$) requires 181.0865; found 181.0870.

X-ray Crystal Structure Determination for (1*RS*,4*RS*,5*SR*)-61

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[44]

X-ray crystal structure data for (1*RS*,4*RS*,5*SR*)-**61** [$C_{10}H_{14}O_3$]: M = 182.22, orthorhombic, space group P 2_1 c n, a = 7.1190(2) Å, b = 10.6793(37) Å, c = 12.0216(42) Å, V = 913.95(5) Å^3, Z = 4, μ = 0.097 mm^{-1}, colourless plate, crystal dimensions = 0.1 × 0.1 × 0.2 mm. A total of 1113 unique reflections were measured for $5 < \theta < 27$ and 1008 reflections were used in the refinement. The final parameters were wR_2 = 0.035 and R_1 = 0.029 [$I>3.0\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC650320. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

(*S*)-7a-Methyl-2,3,7,7a-tetrahydro-(6*H*)-indene-1,5-dione 11



Following *General Procedure 2*, *trans*-β-amino tetrazole (1'*R*,2'*S*)-**60** (20 mg, 0.13 mmol) was added to triketone **9** (79 mg, 0.44 mmol) in anhydrous DMF (1.0 mL). After 1 day a 0.5 mL aliquot was removed

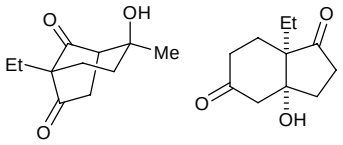
[42] (1*RS*,4*RS*,5*SR*)-**61** was shown to be racemic from 400 MHz ^{1}H NMR spectroscopic analysis in the presence of chiral solvating agent (*R*)-*O*-acetylmandelic acid.

[43] Alcohol **61** has previously been reported but not fully characterized in W. G. Dauben and R. A. Bunce, *J. Org. Chem.*, 1983, **48**, 4642.

[44] P. W. Betteridge, J. R. Carruthers, R. I. Cooper, C. K. Prout and D. J. Watkin, CRYSTALS, 2001, Issue 11, Chemical Crystallography Laboratory, University of Oxford, UK.

and worked-up. Purification of the residue via flash column chromatography (eluent Et_2O) furnished **10** (36 mg, 90 %) as a pale yellow oil; $[\alpha]_D^{22}$ +9.2 (*c* 0.9 in $CHCl_3$) {lit.,[45] *ent*. $[\alpha]_D^{23}$ –57.6 (*c* 0.8 in $CHCl_3$)}. Following *General Procedure 2*, ketol **10** (36 mg, 0.20 mmol) and *p*-TsOH (4 mg, 0.02 mmol) in toluene (2.0 mL) furnished enone (*S*)-**11** in 20 % e.e.[46] (28 mg, 86 %) as a pale yellow solid after flash column chromatography (eluent Et_2O); mp 53-57 ºC (lit.,[45] mp 61-63 ºC); $[\alpha]_D^{22}$ +20.4 (*c* 1.0 in toluene) {lit.,[45] *ent*. $[\alpha]_D^{23}$ –315 (*c* 1.1 in toluene)}.

(1*RS*,4*RS*,5*SR*)-1-Ethyl-5-methyl-5-hydroxy-bicyclo[3.2.1]octan-2,8-dione 62 and (*R*)-7a-Ethyl-2,3,7,7a-tetrahydro-(6*H*)-indene-1,5-dione 47



Following *General Procedure 2*, *cis*-β-amino tetrazole (1'*R*,2'*S*)-**59** (23 mg, 0.15 mmol) was added to triketone **46** (98 mg, 0.50 mmol) in anhydrous DMF (1.5 mL). After 4 days a 0.5 mL aliquot was removed and worked-up to furnish a 19:64:17 mixture of **46**, **62** and **63**. Purifcation via flash column chromatography (eluent 1:1 30-40 petrol: Et_2O) furnished returned starting material **46** (2 mg, 6 %) as a pale yellow oil and a mixed fraction containing **62** and **63** in an 80:20 ratio respectively (28 mg), recrystallisation (Et_2O/*n*-heptane) of this mixture furnished racemic[47] **62** (9 mg, 27 %) as a white crystalline solid;[48] mp 140-143 ºC (lit.,[49] mp 144-153 ºC); ν_{max}/cm^{-1} (KBr disc) 3421 (O–H), 1764, 1725 (2 × C=O); δ_H (500 MHz, $CDCl_3$) 0.83 (3H, t, *J* 7.4, CH_2CH_3), 1.40 (3H, s, C(5)CH_3), 1.56-1.76 (4H, m, CH_2CH_3, C(6)H_2), 1.78-1.85 (1H, m, C(7)H_AH_B), 2.08-2.19 (3H, m, C(7)H_AH_B, O*H*), 2.56-2.60 (2H, m, C(3)H_2), 2.74-2.77 (1H, m, C(4)*H*); δ_C (125 MHz, $CDCl_3$) 9.0 (CH_2CH_3), 20.8 (CH_2CH_3) 28.4 (C(5)CH_3), 32.1 (*C*(6)H_2), 37.4 (*C*(7)H_2), 43.2 (*C*(3)H_2), 57.5 (*C*(4)H), 62.5 (*C*(1)Et), 80.7 (*C*(5)CH_3), 211.4, 214.0 (*C*(2)O, *C*(8)O); *m/z* (GC ToF CI^+) 197 ($[M+H]^+$, 100 %); HRMS (GC ToF CI^+) $C_{11}H_{17}O_3$ ($[M+H]^+$) requires 197.1178 found 197.1179. The supernatant was concentrated *in vacuo* to furnish a

[45] L. G. Sevillano, C. P. Melero, E. T. F. Caballero, L. G. Lelievre, K. Geering, G. Crambert, R. Carron, M. Medarde and A. S. Feliciano, *J. Med. Chem.*, 2002, **45**, 127.
[46] The e.e. of enone **11** was determined using chiral GC analysis; ThermoQuest TRACE GC, fitted with a Cydex-β column, 120 ºC isotherm, 120 min and comparison with an authentic racemic sample, (*R*)-**11** t_R = 91.5 min, (*S*)-**11** t_R = 100.5 min.
[47] (1*RS*,4*RS*,5*SR*)-**62** was shown to be racemic from 400 MHz ^1H NMR spectroscopic analysis in the presence of chiral solvating aent (*R*)-*O*-acetylmandelic acid.
[48] Alcohol **62** has previously been reported but not fully characterized in J. H. Gardner, B. A. Anderson and E. P. Oliveto, *J. Org. Chem.*, 1969, **34**, 107.
[49] J. H. Gardner, B. A. Anderson and E. P. Oliveto, *J. Org. Chem.*, 1969, **34**, 107.

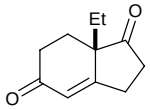
64:36 mixture of **62** and **63** (19 mg). Following *General Procedure 2*, this mixture was treated with *p*-TsOH (2 mg, 0.01 mmol) in toluene (2.0 mL) to furnish enone (*R*)-**47** in 12 % e.e.[50] (17 mg, 98 %) as a brown oil; $[\alpha]_D^{23}$ –33.8 (*c* 0.45 in $CHCl_3$).

X-ray Crystal Structure Determination for (1*RS*,4*RS*,5*SR*)-62

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[51]

X-ray crystal structure data for (1*RS*,4*RS*,5*SR*)-**62** [$C_{11}H_{16}O_3$]: M = 196.25, monoclinic, space group P 1 2_1/c 1, a = 6.9811(2) Å, b = 7.5933(2) Å, c = 19.5994(6) Å, β = 94.874(1)º, V = 1035.20(5) Å^3, Z = 4, μ = 0.090 mm^{-1}, colourless block, crystal dimensions = 0.2 × 0.2 × 0.2 mm. A total of 2341 unique reflections were measured for $5 < \theta < 27$ and 1610 reflections were used in the refinement. The final parameters were wR_2 = 0.048 and R_1 = 0.039 [I>3.0σ(I)]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC650321. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

(*S*)-7a-Ethyl-2,3,7,7a-tetrahydro-(6*H*)-indene-1,5-dione 47



Following *General Procedure 2*, *trans*-β-amino tetrazole (1'*S*,2'*S*)-**60** (30 mg, 0.12 mmol) was added to triketone **46** (128 mg, 0.65 mmol) in anhydrous DMF (2.0 mL). After 1 day a 1.0 mL aliquot was removed and worked-up to furnish a 11:89 mixture of **46** and **63** respectively. Purification of the residue via flash column chromatography (eluent 1:1 30-40 petrol: Et_2O) furnished returned starting material **46** (7 mg, 11 %) as a pale yellow oil, further elution furnished ketol **63** (51 mg, 80 %) as a pale yellow oil.

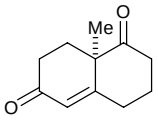
---

[50] The e.e. of enone **47** was determined using chiral GC analysis; ThermoQuest TRACE GC, fitted with a Cydex-β column, 130 ºC isotherm, 120 min and comparison with an authentic racemic sample, (*R*)-**47** t_R = 85.0 min, (*S*)-**47** t_R = 88.2 min.

[51] P. W. Betteridge, J. R. Carruthers, R. I. Cooper, C. K. Prout and D. J. Watkin, CRYSTALS, 2001, Issue 11, Chemical Crystallography Laboratory, University of Oxford, UK.

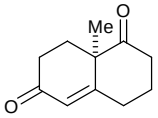
Following *General Procedure 2*, ketol **63** (15 mg, 0.08 mmol) and *p*-TsOH (1.5 mg, 7 μmol) in toluene (2.0 mL) furnished enone (*S*)-**47** in 7 % e.e.[52] (11 mg, 81 %) as a pale yellow oil after flash column chromatography (eluent Et_2O); $[\alpha]_D^{21}$ +18.0 (*c* 0.3 in $CHCl_3$).

(*R*)-8a-Methyl-3,4,8,8a-tetrahydronapthalene-(2*H*,7*H*)-1,6-dione 49



Following *General Procedure 2*, *cis*-β-amino tetrazole (1'*R*,2'*S*)-**59** (14 mg, 0.09 mmol) was added to triketone **48** (60 mg, 0.31 mmol) in anhydrous DMF (0.9 mL). After 2 days a 0.45 mL aliquot was removed and worked-up to furnish enone (*R*)-**49** in 40 % e.e.[53] (22 mg, 81 %) as a pale brown oil after flash column chromatography (eluent Et_2O); $[\alpha]_D^{22}$ –26.0 (*c* 0.5 in EtOH) {lit.,[54] $[\alpha]_D^{25}$ –130 (*c* 0.7, EtOH)}.

(*R*)-8a-Methyl-3,4,8,8a-tetrahydronapthalene-(2*H*,7*H*)-1,6-dione 49



Following *General Procedure 2*, *trans*-β-amino tetrazole (1'*S*,2'*S*)-**60** (19 mg, 0.12 mmol) was added to triketone **48** (81 mg, 0.41 mmol) in anhydrous DMF (1.0 mL). After 5 days a 0.5 mL aliquot was removed and worked-up to furnish returned starting material **48** (4 mg, 10 %) and enone (*R*)-**49** in 28 % e.e.[53] (25 mg, 67 %) as a pale brown oil after flash column chromatography (eluent Et_2O); $[\alpha]_D^{23}$ –27.6 (*c* 0.7 in EtOH) {lit.,[54] $[\alpha]_D^{25}$ –130 (*c* 0.7, EtOH)}.

[52] The e.e. of enone **47** was determined using chiral GC analysis; ThermoQuest TRACE GC, fitted with a Cydex-β column, 130 ºC isotherm, 120 min and comparison with an authentic racemic sample, (*R*)-**47** t_R = 85.0 min, (*S*)-**47** t_R = 88.2 min.

[53] The e.e. of enone **49** was determined using chiral GC analysis; ThermoQuest TRACE GC, fitted with a Cydex-β column, 110 ºC isotherm, 300 min and comparison with an authentic racemic sample, (*R*)-**49** t_R = 260.8 min, (*S*)-**49** t_R = 277.5 min.

[54] V. Prelog and W. Acklin, *Helv. Chim. Acta.*, 1956, **39**, 748.