Asymmetric Synthesis of (−)-(1*R*,2*S*)-Cispentacin and Related *cis*- and *trans*-2-Amino Cyclopentane- and Cyclohexane-1-carboxylic Acids

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The antifungal antibiotic (−)-(1*R*,2*S*)-2-aminocyclopentane-1-carboxylic acid (cispentacin) **8** and its cyclohexane homologue **14** have been prepared utilizing the highly stereoselective conjugate addition of homochiral lithium *N*-benzyl-*N*-α-methylbenzylamide **5**. The corresponding *trans*-β-amino acids **10** and **16** were also prepared *via* the selective epimerization of the *cis*-β-amino ester conjugate addition products.

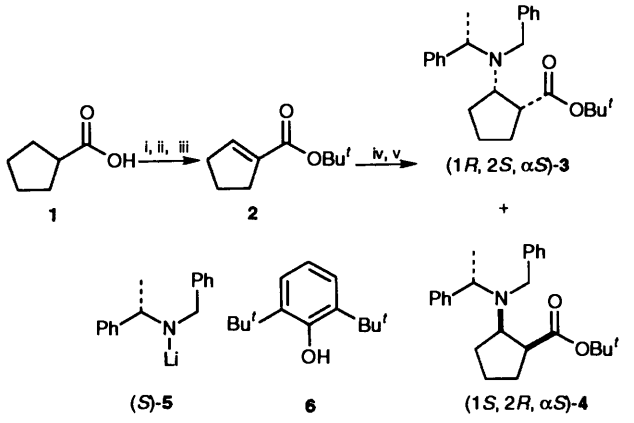
In the course of our investigations into the diastereoselective conjugate additions of homochiral lithium amides,[1] we have begun investigating the enantioselective preparation of α-alkyl-β-amino acids. Such compounds are incorporated in a wide variety of natural products,[2] many of which exhibit interesting biological properties. In particular, (−)-(1*R*,2*S*)-2-amino-cyclopentane-1-carboxylic acid **8** (cispentacin) has recently aroused commercial interest since it has been shown to possess potent antifungal activity.[3] Cispentacin has been isolated from the fermentation broths of both *Streptomyces setonii*[3c] and *Bacillus cereus*[3a] and has demonstrated noteworthy therapeutic efficacy against *Candida albicans*, all the more remarkable given its simple structure and the biological inactivity of its (1*S*,2*R*) enantiomer.[3a] Apart from these fermentation procedures, homochiral cispentacin has been prepared by classical[3a,d] and kinetic[4,5] resolution methods. We have previously communicated[6] an expeditious asymmetric synthesis of (−)-(1*R*,2*S*)-cispentacin based on the highly diastereoselective conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (*S*)-**5**. Herein, we give full details of this methodology and illustrate the versatility of this approach by presenting the enantioselective syntheses of both the *cis*- and *trans*-2-amino-cyclopentane- and cyclohexane-1-carboxylic acids.

Results and Discussion

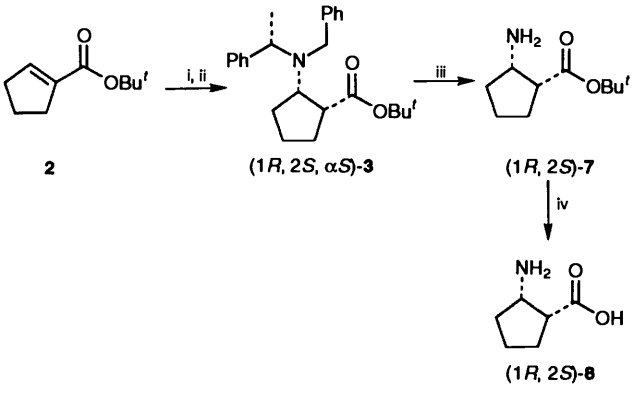
The conjugate acceptor required for the preparation of cispentacin, *tert*-butyl cyclopent-1-enecarboxylate **2**, was first synthesized. Esterification of cyclopentanecarboxylic acid **1** followed by iodination and elimination of hydrogen iodide from the resultant α-iodo ester afforded the α,β-unsaturated ester **2** in 36% overall yield.

The procedure developed[7] for the conjugate addition–protonation of the lithium amide **5** with acyclic α-alkyl acceptors gave disappointing results when applied to compound **2**. Thus, addition of the acceptor **2** to a solution of lithium amide (*S*)-**5** in toluene at −78 °C followed by dilution with THF and quenching with 2,6-di-*tert*-butylphenol **6** gave a 6:1 mixture of the conjugate adduct diastereoisomers (1*R*,2*S*,α*S*)-**3** and (1*S*,2*R*,α*S*)-**4** in 85% yield (Scheme 1).

Repetition of the conjugate addition solely in THF at −95 °C afforded, however, the desired product (1*R*,2*S*,α*S*)-**3** $[\alpha]_D^{25}$ −69.1 (*c* 1.14 in $CHCl_3$) in >98% diastereoisomeric excess, albeit in the reduced yield of 65% (Scheme 2). Debenzylation of the conjugate adduct (1*R*,2*S*,α*S*)-**3** was easily accomplished by hydrogenolysis over palladium on carbon to furnish the free amino ester (1*R*,2*S*)-**7** $[\alpha]_D^{25}$ −5.6 (*c* 0.63 in $CHCl_3$) in 75% yield. Hydrolysis with trifluoroacetic acid followed by ion exchange chromatography then yielded analytically pure cispentacin (1*R*,2*S*)-**8** $[\alpha]_D^{23}$ −8.8 (*c* 1.0 in H_2O) [lit.,[5] $[\alpha]_D$ −8



Scheme 1 *Reagents:* i, 2-methylpropene, H_2SO_4; ii, LDA, I_2; iii, DBU; iv, (*S*)-**5** in toluene then THF; v, 2,6-di-*tert*-butylphenol **6**

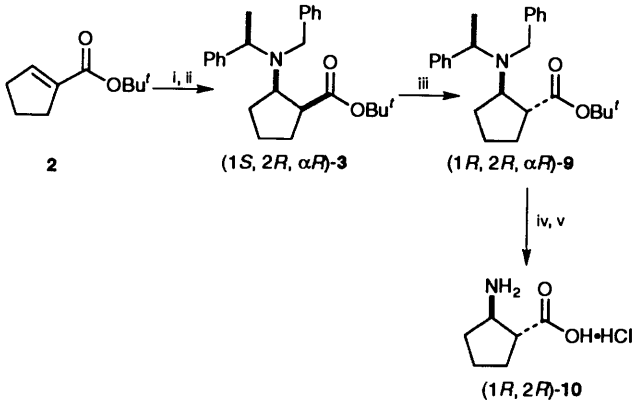


Scheme 2 *Reagents:* i, (*S*)-**5** in THF; ii, 2,6-di-*tert*-butylphenol **6**; iii, H_2, Pd–C; iv, TFA then Dowex 50X8-200

(*c* 1 in H_2O); lit.,[3d] $[\alpha]_D^{20}$ −8.9 (*c* 1.0 in H_2O); lit.,[3a] $[\alpha]_D^{25}$ −10.7 (*c* 1.0 in H_2O)] in 47% overall yield from compound **2**. Comparison of the sign of the specific rotation of compound **8** with that previously established[3a,d] enabled unambiguous assignment of its absolute configuration as (1*R*,2*S*). An enantiomeric excess of >98% can be assigned to this material since any compromise of stereochemistry would have generated the corresponding *trans*-amino acid. The sense of asymmetric induction observed in this conjugate addition is therefore, as expected, the same as that found in additions to crotonate[1a] and cinnamate[1b] esters and corresponds to chelation-controlled addition to the *re*-face of the α,β-unsaturated ester in the s-*cis* conformation.

The conjugate addition was repeated with the opposite

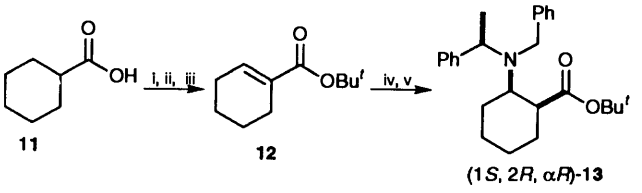
lithium amide enantiomer (*R*)-**5** to give the adduct (1*S*,2*R*,α*R*)-**3** $[\alpha]_D^{25}$ +70.3 (*c* 0.73 in $CHCl_3$). This was selectively epimerized at C-1 in the presence of base of the corresponding *trans*-amino ester (1*R*,2*R*,α*R*)-**9** $[\alpha]_D^{25}$ −72.8 (*c* 2.45 in $CHCl_3$) in 75% yield and >98% d.e. Deprotection of this stereoisomer was similarly straightforward, and the *trans*-β-amino acid (1*R*,2*R*)-**10** $[\alpha]_D^{25}$ −50.7 (*c* 0.75 in H_2O) was isolated in 62% yield as its hydrochloride salt (Scheme 3). This material can also be



Scheme 3 *Reagents:* i, (*R*)-**5** in THF; ii, 2,6-di-*tert*-butylphenol **6**; iii, KHMDS, Bu'OH; iv, H_2, Pd–C; v, TFA then HCl

assumed to be homochiral, since epimerization at the C-2 position is not feasible under basic conditions.

An analogous sequence of reactions was then performed, beginning with cyclohexanecarboxylic acid **11**. After the routine preparation of the cyclohexyl conjugate acceptor **12** (30% overall yield), the conjugate addition was carried out in THF with and without toluene as before (Scheme 4). In this case, no

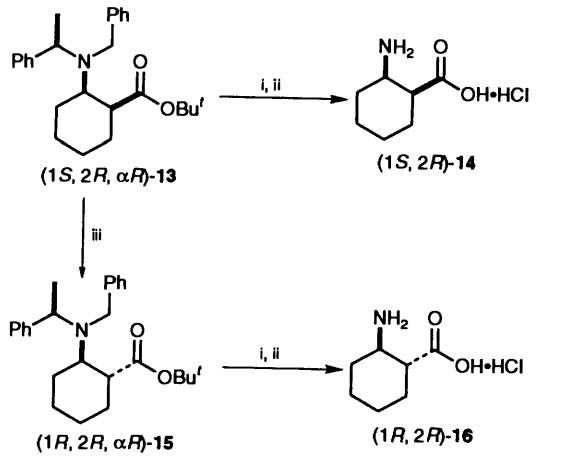


Scheme 4 *Reagents:* i, 2-methylpropene, H_2SO_4; ii, LDA, I_2; iii, DBU; iv, (*R*)-**5** in toluene then THF; v, 2,6-di-*tert*-butylphenol **6**

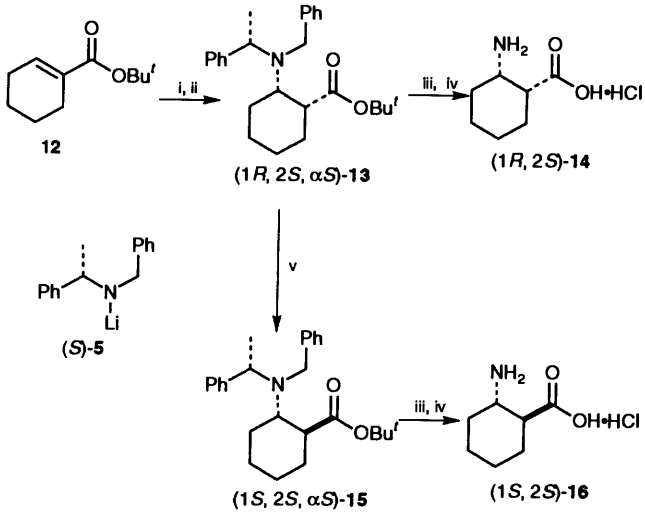
difference was observed in either the reaction yield (70%) or diastereomeric excess (>95%). The absolute and relative stereochemistry of the *cis*-cyclohexyl amino ester adduct (1*S*,2*R*,α*R*)-**13** $[\alpha]_D^{25}$ +88.3 (*c* 1.00 in $CHCl_3$) was assigned by analogy to the cyclopentyl product (1*R*,2*S*,α*S*)-**3**.

Deprotection of the adduct (1*S*,2*R*,α*R*)-**13** under standard conditions afforded (1*S*,2*R*)-2-aminocyclohexane-1-carboxylic acid hydrochloride (1*S*,2*R*)-**14** $[\alpha]_D^{25}$ +1.7 (*c* 0.60 in MeOH) in good yield (71%) (Scheme 5). Epimerization of the adduct (1*S*,2*R*,α*R*)-**13** furnished the C-1 epimer (1*R*,2*R*,α*R*)-**15** $[\alpha]_D^{25}$ −29.6 (*c* 1.02 in $CHCl_3$) (97% yield, 97% d.e.) which gave the corresponding *trans*-amino acid hydrochloride (1*R*,2*R*)-**16** $[\alpha]_D^{25}$ −45.4 (*c* 1.04 in H_2O) in 56% yield upon debenzylation and hydrolysis (Scheme 5).

These reactions were then all repeated using the enantiomeric lithium amide (*S*)-**5** (Scheme 6). Thus, the conjugate addition of (*S*)-**5** to compound **12** generated (1*R*,2*S*,α*S*)-**13** $[\alpha]_D^{25}$ −92.0 (*c* 1.00 in $CHCl_3$) in >95% d.e., and subsequent deprotection afforded the amino acid (1*R*,2*S*)-**14** $[\alpha]_D^{25}$ −1.0 (*c* 0.59 in MeOH). Epimerization of (1*R*,2*S*,α*S*)-**13** gave (1*S*,2*S*,α*S*)-**15** $[\alpha]_D^{25}$ +30.4 (*c* 1.00 in $CHCl_3$) in 97% d.e. which was subsequently debenzylated and hydrolysed to form the *trans*-amino acid hydrochloride (1*S*,2*S*)-**16** $[\alpha]_D^{25}$ +47.4 (*c* 1.14 in H_2O).



Scheme 5 *Reagents:* i, H_2, Pd–C; ii, TFA then HCl; iii, KHMDS, Bu'OH



Scheme 6 *Reagents:* i, (*S*)-**5** in THF; ii, 2,6-di-*tert*-butylphenol **6**; iii, H_2, Pd–C; iv, TFA then HCl; v, KHMDS, Bu'OH

The simple preparation of homochiral *cis*- and *trans*-β-amino-cyclopentane- and cyclohexane-carboxylic acids described herein testifies to the efficiency and flexibility of this lithium amide conjugate addition protocol. We have shown that any stereoisomer of these amino acids of predetermined relative and absolute stereochemistry can be easily accessed. This method can be readily scaled-up and should be suitable for preparing a variety of structural analogues.

Experimental

Specific rotations were determined using a Perkin-Elmer 241 polarimeter with a thermally jacketted 10-cm cell and are reported in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed by the Dyson Perrins analytical department. Melting points were recorded on a Gallenkamp hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer either as chloroform solutions in 1.0 mm NaCl cells or as Nujol mulls. Unless otherwise stated, all NMR spectra were recorded using samples dissolved in deuteriochloroform and referenced with respect to residual protio solvent as an internal standard. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ 0.00 ppm) and coupling constants are measured in Hz. Three instruments were used to obtain ^1H NMR spectra, a Varian Gemini 200 and Bruker AM500 and WH300 spectrometers, with the former two also providing ^{13}C NMR

spectra with DEPT editing. Mass spectra were recorded on a VG MASSLAB VG 20-250 instrument. Flash column chromatography was performed on silica gel (Kieselgel 60) or Dowex 50X8-200 resin. Tetrahydrofuran and toluene were distilled from sodium benzophenone ketyl under an atmosphere of dry nitrogen. Petroleum refers to light petroleum (b.p. 40–60 °C), redistilled before use. Reactions involving lithium amides were performed under an atmosphere of dry nitrogen. The conjugate additions were performed with homochiral (>98% e.e.) *N*-benzyl-*N*-α-methylbenzylamine,[8] according to ^{1}H NMR chiral shift studies with *O*-acetylmandelic acid.[9] In every case, reaction diastereoselectivities were determined by peak integration of the crude reaction products' ^{1}H NMR spectra.

tert-*Butyl Cyclopent*-1-*ene*-1-*carboxylate* **2**.—2-Methylpropene (30 cm^3) was condensed into a solution of cyclopentanecarboxylic acid **1** (10.0 g, 87.7 mmol) and conc. sulfuric acid (1 cm^3) in dichloromethane (50 cm^3) at −78 °C. The reaction mixture was allowed to warm slowly to room temperature over a period of 20 h and then extracted from sat. aq. $NaHCO_3$ with diethyl ether (3 × 50 cm^3). The organic phase was dried, concentrated and then filtered through a plug of silica with petroleum–diethyl ether (10:1) to give *tert*-butyl cyclopentanecarboxylate as a colourless oil (13.5 g). A solution of this ester (12.0 g, 70.6 mmol) in precooled THF (−78 °C, 20 cm^3) was then added by cannula over 5 min to a solution of lithium diisopropylamide (LDA) (106 mmol) in THF (100 cm^3) at −78 °C and the reaction mixture stirred at this temperature for 1 h. The enolate solution was then transferred by cannula into a solution of iodine (30.5 g, 120 mmol) in THF (100 cm^3) at −78 °C. The reaction was stirred at −78 °C for a further 30 min before conc. HCl (20 cm^3) was added and the resultant brown solution warmed to room temperature. Evaporation of solvent gave a residue which was partitioned between diethyl ether and aq. sodium thiosulfate. The organic phase was dried ($MgSO_4$), filtered and concentrated to give an orange oil (14.1 g). To a solution of this material (11.0 g) in THF (100 cm^3) at 0 °C was added dropwise by cannula a solution of 1,8-diazabicyclo[4.5.0]undec-7-ene (DBU) (9.0 g, 59.5 mmol) in THF (20 cm^3). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for a further 48 h. The residue obtained on solvent evaporation was partitioned between diethyl ether and water, the organic phase dried, filtered and concentrated to give a pale yellow oil. Flash column chromatography on silica gel with a petroleum–diethyl ether (100:1) eluent afforded the α,β-unsaturated ester **2** as a colourless oil (4.30 g), contaminated with 15% of *tert*-butyl cyclopentanecarboxylate. Allowing for this contamination, the overall yield of compound **2** was 36%. Pure compound **2** was obtained by preparative gas chromatography: Pye Unicam Series 105 Chromatograph; Chromosorb A column, 7 ft long, 0.375 in diam., PEG 20M; N_2 carrier gas, 20 lb in^{-2}, 180 cm^3/min^{-1}; 250 mm^3 injection; oven temperature 170 °C, injection 220 °C; δ_H(lit.,[10] 300 MHz; $CDCl_3$) 6.67 (1 H, m, CHCCO), 2.57–2.44; 1.99–1.89 [6 H, m, $(CH_2)_3$] and 1.49 (9 H, s, CMe_3).

General Procedures for Lithium Amide Conjugate Additions.—(*a*) *Toluene–THF solvent*. A solution of *N*-benzyl-*N*-α-methylbenzylamine[8] (3.2 mmol) in toluene (4 cm^3) was cooled to 0 °C prior to the slow addition of butyllithium (1.6 mol dm^{-3}; 3.0 mmol). The resultant pink solution of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **5** (3.0 mmol) was stirred for 15 min then cooled to −78 °C, after which a toluene (2 cm^3) solution of the requisite conjugate acceptor (2.0 mmol) was added dropwise by syringe. The reaction mixture was stirred for 1 h at −78 °C, then maintained at −30 °C for 2 h, before being recooled to −78 °C. Precooled THF (−78 °C, 20 cm^3) was added swiftly by cannula and the reaction mixture stirred for a further 30 min at −78 °C. Finally, a solution of 2,6-di-*tert*-butylphenol **6** (6.0 mmol) in THF (2 cm^3) was added by syringe, and the reaction mixture allowed to warm to room temperature over 30 min. Evaporation of the solvent under reduced pressure left a residue which was partitioned between brine (50 cm^3) and diethyl ether (50 cm^3), and the organic phase dried over $MgSO_4$, filtered and concentrated to give the crude conjugate adduct.

(*b*) *THF solvent*. The reaction was performed as in (*a*) but using THF (10 cm^3) rather than toluene (4 cm^3), thus obviating the need for dilution of the reaction mixture with THF prior to quenching with the phenol **6**.

General Debenzylation–Hydrolysis Procedure.—(*c*) The requisite conjugate adduct (1.0 mmol) and Pd–C (10% Pd content, 30% by mass) were placed in a Fischer–Porter bottle which was flushed with argon prior to charging with acetic acid (5 cm^3). The reaction mixture was placed under a hydrogen atmosphere (4 bar) and stirred vigorously at 50 °C overnight, after which it was filtered through a plug of Celite, washed through with methanol and concentrated to give a white solid. This residue was partitioned between sat. aq. $NaHCO_3$ (25 cm^3) and dichloromethane (25 cm^3) and the organic phase dried ($MgSO_4$). This solution was filtered and acidified with sat. HCl in diethyl ether (5 cm^3) and then evaporated to give a white solid which was washed with diethyl ether. This solid was dissolved in trifluoroacetic acid (4 cm^3) and the solution stirred at room temperature for 15 h. Evaporation gave an oil which was dissolved in a mixture of methanol (2 cm^3) and sat. HCl in diethyl ether (2 cm^3). Concentration of this solution afforded the crude β-amino acid as its hydrochloride salt.

General Procedure for Epimerization of Conjugate Adducts.—(*d*) A solution of *tert*-butyl alcohol (11.0 mmol) in THF (20 cm^3) was cooled to 0 °C prior to the slow addition of potassium bis(trimethylsilyl)amide (5.00 mmol, 0.66 mol dm^{-3} in toluene). After this solution had been stirred at 0 °C for 15 min, a solution of the requisite conjugate adduct (1.30 mmol) in THF (5 cm^3) was added to it and the reaction mixture stirred at room temperature for 6 d. The residue obtained on evaporation of solvent was partitioned between brine (50 cm^3) and diethyl ether (50 cm^3) and the organic phase dried ($MgSO_4$), filtered and evaporated to give the crude product as a colourless oil.

tert-*Butyl* 2-(N-*Benzyl*-N-α-*methylbenzylamino*)*cyclopentane carboxylate* (1R,2S,αS)-**3** *and* (1S,2R,αS)-**4**.—The conjugate addition of the lithium amide (*S*)-**5** (26.8 mmol) to *tert*-butyl cyclopent-1-enecarboxylate **2** (2.55 g, 15.2 mmol) was carried out according to the general procedure (*a*), to give the two diastereoisomeric adducts (1*R*,2*S*,α*S*)-**3** and (1*S*,2*R*,α*S*)-**4** in the ratio of 6:1. Flash column chromatography of the crude product on silica gel with a petroleum–diethyl ether (20:1) eluent provided a pure sample of (1*R*,2*S*,α*S*)-**3** (2.72 g, 47%) and a sample enriched in (1*S*,2*R*,α*S*)-**4** (310 mg, 78% d.e.), both as colourless oils, in addition to a mixed fraction (overall yield 85%).

The conjugate addition of the lithium amide (*S*)-**5** (1.18 mmol) to *tert*-butyl cyclopent-1-enecarboxylate **2** (124 mg, 0.74 mmol) was carried out according to the general procedure (*b*), except that the addition was performed at −95 °C, and the mixture then warmed gradually to −78 °C over 2 h and finally quenched at −78 °C. This reaction generated the adduct (1*R*,2*S*,α*S*)-**3** in >98% d.e., and chromatography as above afforded the pure product as a colourless oil (182 mg, 65%).

(1*R*,2*S*,α*S*)-**3**. $[\alpha]_D^{25}$ −69.1 (*c* 1.14 in $CHCl_3$) (Found: C, 79.3; H, 8.5; N, 3.6. $C_{25}H_{33}NO_2$ requires C, 79.11; H, 8.76; N, 3.69%); ν_{max}($CHCl_3$)/cm^{-1} 1715 (C=O); δ_H(300 MHz; $CDCl_3$) 7.44–7.16

(10 H, m, Ph), 4.32 (1 H, q, *J* 6.9, MeC*H*N), 4.03 and 3.54 (2 H, AB system, J_{AB} 15.5, PhCH_2N), 3.16–3.08 and 2.95–2.89 (2 H, m, CH_2CHN and $CHCO_2$), 1.84–1.38 [6 H, m, $(CH_2)_3$], 1.52 (9 H, s, CMe_3), 1.39 (3 H, d, *J* 6.9, *Me*CH); δ_C(50 MHz; $CDCl_3$) 175.5 (CO_2), 143.2 and 142.8 (PhC_{ipso}), 128.2, 128.1, 127.0 and 126.4 (Ph), 80.0 (CMe_3), 66.0 and 58.0 (CHN), 51.7 (CH_2N), 48.4 (*C*HCO), 28.2 (CMe_3), 28.9, 27.4 and 22.0 [$(CH_2)_3$] and 17.3 (*Me*CH); *m*/*z* 380 (MH^+, 100%) and 274 (30, MH^+ – $PhCH_2Me$).

(1*S*,2*R*,α*S*)-**4**. (Found: C, 79.1; H, 9.0; N, 4.0, $C_{25}H_{33}NO_2$ requires C, 79.11; H, 8.76; N, 3.69%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1710 (C=O); δ_H(300 MHz; $CDCl_3$) 7.45–7.15 (10 H, m, Ph), 4.22 (1 H, q, *J* 6.9, MeC*H*N), 3.87 and 3.52 (2 H, AB system, J_{AB} 14.7, PhCH_2N), 3.38 (1 H, dt, *J* 6.9 and 10.4, CH_2CHN), 2.96 (1 H, td, *J* 3.4 and 6.9, $CHCO_2$), 1.90–1.40 [6 H, m, $(CH_2)_3$], 1.51 (9 H, s, CMe_3) and 1.43 (3 H, d, *J* 6.9, *Me*CH); δ_C(50 MHz; $CDCl_3$) 175.1 (CO_2), 144.0 and 142.3 (PhC_{ipso}), 128.5, 128.3 and 128.0 (Ph), 126.7 and 126.4 (PhC_{para}), 80.1 (CMe_3), 65.2 and 56.9 (CHN), 52.9 (CH_2N), 49.6 (*C*HCO), 28.2 (CMe_3), 28.9, 27.5 and 22.0 [$(CH_2)_3$] and 12.3 (*Me*CH); *m*/*z* 380 (MH^+, 100%), 105 (30, $PhCHMe^+$) and 91 (30, $PhCH_2^+$).

(1R,2S)-tert-*Butyl* 2-*Aminocyclopentanecarboxylate* (1R,2S)-**7**.—Debenzylation of the conjugate adduct (1*R*,2*S*,α*S*)-**3** (500 mg, 1.32 mmol) was carried out according to the general procedure (*c*). The intermediate primary amino ester (1*R*,2*S*)-**7** was isolated by concentration of the organic phase obtained after partitioning with sat. aq. $NaHCO_3$. Flash column chromatography of this crude product on silica gel with a methanol–diethyl ether (1:1) eluent afforded the pure amino ester (1*R*,2*S*)-**7** as a colourless oil (184 mg, 75%), $[\alpha]_D^{25}$ −5.6 (*c* 0.63 in $CHCl_3$) (Found: C, 54.4; H, 9.3; N, 6.3. $C_{10}H_{19}NO_2$·HCl requires C, 54.17; H, 9.09; N, 6.32%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1715 (C=O); δ_H(300 MHz; $CDCl_3$) 3.59–3.54 (1 H, m, CH_2CHN), 2.74–2.66 (1 H, m, $CHCO_2$), 2.05–1.47 [8 H, m, $(CH_2)_3$, NH_2] and 1.48 (9 H, s, CMe_3); δ_C(50 MHz; $CDCl_3$) 173.8 (CO_2), 80.2 (CMe_3), 54.9 (CHN), 51.0 (*C*HCO), 28.0 (CMe_3), 34.7, 26.0 and 22.2 [$(CH_2)_3$]; *m*/*z* 186 (MH^+, 20%) and 130 (100, MH^+ – $Me_2C{=}CH_2$).

(1R,2S)-2-*Aminocyclopentanecarboxylic Acid* (1R,2S)-**8**.—A solution of the ester (1*R*,2*S*)-**7** (135 mg, 0.73 mmol) in trifluoroacetic acid was stirred at room temperature for 16 h. Evaporation of the solvent gave an oil which was dissolved in methanol (2 cm^3) and sat. HCl in diethyl ether (2 cm^3). The solvent was removed to give a pale brown solid which was partitioned between diethyl ether (5 cm^3) and water (5 cm^3). The aqueous phase was concentrated to half its volume and chromatographed using a Dowex 50X8-200 resin with 1 mol dm^{-3} aq. ammonium hydroxide. The free amino acid (1*R*,2*S*)-**8** was isolated as a white solid (89 mg, 95%), $[\alpha]_D^{23}$ −8.8 (*c* 1.00 in H_2O; lit.,[3a,3d,5]); m.p. (lit.,[3c]) 194–197 (decomp.) (Found: C, 55.7; H, 8.6; N, 10.5. $C_6H_{11}NO_2$ requires C, 55.80; H, 8.58; N, 10.84%); δ_H(lit.,[3d]; 500 MHz; D_2O; DSS*) 3.73–3.70 (1 H, m, C*H*NH_2), 2.88–2.84 (1 H, m, C*H*CO_2H), 2.11–2.05 and 1.86–1.70 [6 H, m, $(CH_2)_3$]; δ_C(lit.,[3c]; 50 MHz; D_2O) 180.8 (CO_2), 52.7 (CHN), 47.2 (*C*HCO), 29.1, 27.6 and 20.8 [$(CH_2)_3$]; *m*/*z* 130 (MH^+, 100%).

(1S,2R,αR)-tert-*Butyl* 2-(N-*Benzyl*-N-α-*methylbenzylamino*)*cyclopentanecarboxylate* (1S,2R,αR)-**3**.—The conjugate addition of the lithium amide (*R*)-**5** (26.8 mmol) to *tert*-butyl cyclopent-1-enecarboxylate **2** (1.65 g, 9.90 mmol) in THF was carried out as described above for the corresponding reaction with the enantiomer (*S*)-**5**. This generated the adduct (1*S*,2*R*,α*R*)-**3** in >98% d.e., and chromatography as before afforded the pure product as a colourless oil (1.80 g, 50%); $[\alpha]_D^{25}$ +70.3 (*c* 0.73 in $CHCl_3$) (Found: C, 79.2; H, 8.4; N, 3.45. $C_{25}H_{33}NO_2$ requires C, 79.11; H, 8.76; N, 3.69%).

tert-*Butyl* (1*R*,2*R*,αR)-2-(N-*Benzyl*-N-α-*methylbenzylamino*)-*cyclopentanecarboxylate* (1R,2R,αR)-**9**.—The epimerization of the adduct (1*S*,2*R*,α*R*)-**3** (1.00 g, 2.63 mmol) to (1*R*,2*R*,α*R*)-**9** was carried out as described in the general procedure (*d*). The crude product containing (1*R*,2*R*,α*R*)-**9** in 98% d.e. was purified by flash column chromatography on silica gel with a petroleum–diethyl ether (30:1) eluent to give the desired product as a colourless oil (0.75 g, 75%), $[\alpha]_D^{25}$ −72.8 (*c* 2.45 in $CHCl_3$) (Found: C, 79.2; H, 9.0; N, 3.6. $C_{25}H_{33}NO_2$ requires C, 79.11; H, 8.76; N, 3.69%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1715 (C=O); δ_H(300 MHz; $CDCl_3$) 7.47–7.18 (10 H, m, Ph), 3.90 (1 H, q, *J* 6.9, MeC*H*N), 3.78 and 3.70 (2 H, AB system, J_{AB} 14.9, PhCH_2N), 3.62–3.54 (1 H, m, CH_2CHN), 2.68–2.60 (1 H, m, $CHCO_2$), 1.80–1.54 [6 H, m, $(CH_2)_3$], 1.39 (9 H, s, CMe_3) and 1.33 (3 H, d, *J* 6.9, *Me*CH); δ_C(50 MHz; $CDCl_3$) 175.9 (CO_2), 144.8 and 142.2 (PhC_{ipso}), 128.6, 128.3, 128.1, 126.8 and 126.7 (Ph), 79.7 (CMe_3), 63.9 and 58.0 (CHN), 50.1 (CH_2N), 49.1 (*C*HCO), 29.4, 28.5 and 24.5 [$(CH_2)_3$], 28.0 (CMe_3) and 16.0 (*Me*CH); *M*/*z* 380 (MH^+, 100%) and 274 (25, MH^+ – $PhCH_2Me$).

(1R,2R)-2-*Aminocyclopentanecarboxylic Acid Hydrochloride* (1R, 2R)-**10**.—Deprotection of the epimerized adduct (1*R*,2*R*, α*R*)-**9** (480 mg, 1.26 mmol) was carried out according to the general procedure (*c*). The amino acid product (1*R*,2*R*)-**10** was isolated as a white solid after recrystallization from water (130 mg, 62%); $[\alpha]_D^{25}$ −50.7 (*c* 0.75 in H_2O); m.p. 150–155 °C (Found: C, 43.3; H, 7.5; N, 8.2. $C_6H_{12}ClNO_2$ requires C, 43.51; H, 7.30; N, 8.46%); δ_H(300 MHz; D_2O; dioxane) 3.87 (1 H, m, C*H*NH_2), 2.90 (1 H, m, C*H*CO_2H), 2.24–2.15 and 1.89–1.68 [6 H, m, $(CH_2)_3$]; δ_C(125 MHz; D_2O; dioxane) 178.3 (CO_2), 54.7 (CHN), 49.4 (*C*HCO), 31.1, 29.4 and 23.4 (CH_2); *m*/*z* 130 (MH^+, 100%).

tert-*Butyl Cyclohex*-1-*enecarboxylate* **12**.—Cyclohexanecarboxylic acid **11** (10.5 g, 82.1 mmol) was converted into the cyclohexyl conjugate acceptor **12** in exactly the same manner as described above for the cyclopentyl analogue **2**. Flash column chromatography of the crude product on silica gel with a petroleum–diethyl ether (100:1) eluent gave compound **12** as a colourless oil (6.36 g), contaminated with 29% of *tert*-butyl cyclohexanecarboxylate. Allowing for this contamination, the overall yield of the acceptor **12** was 30%. Pure compound **12** was obtained by preparative gas chromatography: Pye Unicam Series 105 Chromatograph; Chromosorb A column, 7 ft long, 0.375 in diam., PEG 20M; N_2 carrier gas, 20 lb in^{-2}., 180 cm^3/min; 250 mm^3 injection; oven temperature 180 °C, injection 220 °C. δ_H(lit.,[11]; 500 MHz; CCl_4); 6.76 (1 H, m, CHCCO), 2.18–2.13 and 1.66–1.57 [8 H, m, $(CH_2)_4$] and 1.44 (9 H, s, CMe_3).

(1S,2R,αR)-tert-*Butyl* 2-(N-*Benzyl*-N-α-*methylbenzylamino*)*cyclohexanecarboxylate* (1S,2R,αR)-**13**.—The conjugate addition of the amide (*R*)-**5** (1.65 mmol) to *tert*-butyl cyclohex-1-enecarboxylate **12** (160 mg, 0.88 mmol) was carried out according to the general procedure (*a*). Purification of the crude product, which contained (1*S*,2*R*,α*R*)-**13** in >95% d.e., by flash column chromatography on silica gel with a petroleum–diethyl ether (30:1) eluent afforded the conjugate adduct (1*S*,2*R*,α*R*)-**13** as a white crystalline solid (243 mg, 70%), subsequently recrystallized from methanol. Repetition of the reaction according to procedure (*b*) was found to make no difference to reaction yield or selectivity in this case; $[\alpha]_D^{25}$ +88.3 (*c* 1.00 in $CHCl_3$); m.p. 59–60 °C (Found: C, 79.6; H, 9.1;

* DSS = sodium 3-(trimethylsilyl)-1-propenesulfonate.

N, 3.3. $C_{26}H_{35}NO_2$ requires C, 79.35; H, 8.96; N, 3.56%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1715 (C=O); δ_H(300 MHz; $CDCl_3$) 7.49–7.18 (10 H, m, Ph), 4.03 (1 H, q, *J* 6.7, MeC*H*N), 4.03 and 3.86 (2 H, AB system, J_{AB} 14.8, PhCH_2*N*), 2.64 (1 H, ddd, *J* 12.6, 4.1 and 4.1, CH_2CHN), 2.47 (1 H, m, $CHCO_2$), 2.22 (1 H, qd, *J* 3.6 and 12.6, $CH_{ax}H_{eq}CHN$), 1.84–1.79, 1.70–1.49 and 1.40–1.14 [7 H, m, $(CH_2)_3CH_{ax}H_{eq}CHN$], 1.45 (9 H, s, CMe_3), 1.31 (3 H, d, *J* 6.7, *Me*CH); δ_C(50 MHz; $CDCl_3$) 175.5 (CO_2), 144.9; 142.9 (PhC_{ipso}), 128.5, 128.2 and 128.1 (Ph), 126.6 and 126.6 (PhC_{para}), 79.8 (CMe_3), 58.5 and 56.5 (CHN), 51.1 (CH_2N), 46.0 (*C*HCO), 28.1 (CMe_3), 29.4, 26.3, 26.3 and 20.9 [$(CH_2)_4$] and 14.2 (*Me*CH); *m*/*z* 394 (MH^+, 100%).

(1S,2R)-2-*Aminocyclohexanecarboxylic Acid Hydrochloride* (1S,2R)-**14**.—Deprotection of the adduct (1*S*,2*R*,α*R*)-**13** (340 mg, 0.86 mmol) was carried out according to the general procedure (*c*). The amino acid product (1*S*,2*R*)-**14** was isolated as a white solid after recrystallization from ethanol (111 mg, 71%); $[\alpha]_D^{25}$ +1.7 (*c* 0.60 in MeOH); m.p. (lit.,[12]) 230–235 °C (dec.) (Found: C, 46.8; H, 8.0; N, 8.0. $C_7H_{14}ClNO_2$ requires C, 46.80; H, 7.86; N, 7.80%); ν_{max}(Nujol mull)/cm^{-1} 1700, 1560, 1020 and 720; δ_H(lit.,[13] 300 MHz; D_2O; dioxane) 3.57 (1 H, m, C*H*NH_2), 2.99 (1 H, m, C*H*CO_2H), 2.05–1.43 [8 H, m, $(CH_2)_4$]; δ_C(125 MHz; D_2O) 177.3 (CO_2), 50.5 (CHN), 42.6 (*C*HCO), 27.8, 26.4, 22.6 and 22.6 (CH_2); *m*/*z* 144 (MH^+, 100%).

tert-*Butyl* (1*R*,2*R*,α*R*)-2-(N-*Benzyl*-N-α-*methylbenzylamino*)-*cyclohexane*-1-*carboxylate* (1R,2R,α*R*)-**15**.—The epimerization of the adduct (1*S*,2*R*,α*R*)-**13** (500 mg, 1.27 mmol) to (1*R*,2*R*,α*R*)-**15** was carried out as described in the general procedure (*d*). The crude product containing (1*R*,2*R*,α*R*)-**15** in >97% d.e. was purified by flash column chromatography on silica gel with a petroleum–diethyl ether (30:1) eluent to give the desired product as a colourless oil (485 mg, 97%); $[\alpha]_D^{25}$ −29.6 (*c* 1.02 in $CHCl_3$) (Found: C, 79.3; H, 9.0; N, 3.6. $C_{26}H_{35}NO_2$ requires C, 79.35; H, 8.96; N, 3.56%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O); δ_H(300 MHz; $CDCl_3$) 7.34–7.18 (10 H, m, Ph), 4.08 (1 H, q, *J* 6.9, MeC*H*N), 3.75 and 3.71 (2 H, AB system, J_{AB} 14.5, PhCH_2N), 3.04 (1 H, ddd, *J* 3.4, 11.4 and 11.4, CH_2CHN), 2.22 (1 H, ddd, *J* 3.6, 11.4 and 11.4, $CHCO_2$), 1.80–1.20 [8 H, m, $(CH_2)_4$], 1.47 (9 H, s, CMe_3) and 1.38 (3 H, d, *J* 6.9, *Me*CH); δ_C(50 MHz; $CDCl_3$) 175.3 (CO_2), 144.9 and 142.2 (PhC_{ipso}), 129.1, 128.2 and 128.0 (Ph), 126.7 and 126.6 (PhC_{para}), 79.5 (CMe_3), 60.1 and 59.9 (CHN), 50.1 (*C*HCO), 49.5 (CH_2N), 28.1 (CMe_3), 30.6, 27.9, 25.7 and 25.1 [$(CH_2)_4$] and 18.9 (*Me*CH); *m*/*z* 394 (MH^+, 100%), 105 (40, $PhCHMe^+$) and 91 (40, $PhCH_2^+$).

(1R,2R)-2-*Aminocyclohexanecarboxylic Acid Hydrochloride* (1R,2R)-**16**.—Deprotection of the adduct (1*R*,2*R*,α*R*)-**15** (290 mg, 0.74 mmol) was carried out according to the general procedure (*c*). The amino acid product (1*R*,2*R*)-**16** was isolated as a white solid after recrystallization from ethanol (74 mg, 56%); $[\alpha]_D^{25}$ −45.4 (*c* 1.04 in H_2O); m.p. (lit.,[12]) 202–206 °C (decomp.) (Found: C, 46.8; H, 7.9; N, 7.9. $C_7H_{14}ClNO_2$ requires C, 46.80; H, 7.86; N, 7.80%); ν_{max}(Nujol mull)/cm^{-1} 1700, 1020, 740 and 720; δ_H(300 MHz; D_2O; dioxane) 3.38 (1 H, m, C*H*NH_2), 2.50 (1 H, m, C*H*CO_2H), 2.19–1.30 [8 H, m, $(CH_2)_4$]; δ_C(125 MHz; D_2O) 177.8 (CO_2), 51.7 (CHN), 46.8 (*C*HCO), 30.2, 29.1, 24.7 and 24.2 (CH_2); *m*/*z* 144 (MH^+, 100%).

(1R,2S,αS)-tert-*Butyl* 2-(N-*Benzyl*-N-α-*methylbenzyl-amino*)*cyclohexanecarboxylate* (1R,2S,αS)-**13**.—The conjugate addition of the lithium amide (*S*)-**5** (33.0 mmol) to *tert*-butyl cyclohex-1-enecarboxylate **12** (3.14 g, 17.2 mmol) was carried out according to the general procedure (*a*). Purification as described above for its enantiomer furnished compound (1*R*,2*S*,α*S*)-**13** as a white crystalline solid (4.26 g, 63%); $[\alpha]_D^{25}$ −92.0 (*c* 1.00 in $CHCl_3$) (Found: C, 79.1; H, 9.3; N, 3.35. $C_{26}H_{35}NO_2$ requires C, 79.35; H, 8.96; N, 3.56%).

(1R,2S)-2-*Aminocyclohexanecarboxylic Acid Hydrochloride* (1R,2S)-**14**.—Deprotection of the adduct (1*R*,2*S*,α*S*)-**13** (583 mg, 1.48 mmol) was carried out according to the general procedure (*c*). The amino acid product (1*R*,2*S*)-**14** was isolated as a white solid after recrystallization from ethanol (180 mg, 68%); $[\alpha]_D^{25}$ −1.0 (*c* 0.59 in MeOH) (Found: C, 46.8; H, 8.2; N, 7.8. $C_7H_{14}ClNO_2$ requires C, 46.80; H, 7.86; N, 7.80%).

(1S,2S,αS)-tert-*Butyl* 2-(N-*Benzyl*-N-α-*methylbenzyl-amino*)*cyclohexanecarboxylate* (1S,2S,αS)-**15**.—The epimerization of the adduct (1*R*,2*S*,α*S*)-**13** (900 mg, 2.29 mmol) to (1*S*,2*S*,α*S*)-**15** was carried out as described in the general procedure (*d*). Purification as described above for its enantiomer furnished the desired compound as a colourless oil (700 mg, 78%); $[\alpha]_D^{25}$ +30.4 (*c* 1.00 in $CHCl_3$) (Found: C, 79.5; H, 9.15; N, 3.75. $C_{26}H_{35}NO_2$ requires C, 79.35; H, 8.96; N, 3.56%).

(1S,2S)-2-*Aminocyclohexanecarboxylic Acid Hydrochloride* (1S,2S)-**16**.—Deprotection of the epimerized adduct (1*S*,2*S*,α*S*)-**15** (600 mg, 1.52 mmol) was carried out according to the general procedure (*c*). The amino acid product (1*S*,2*S*)-**16** was isolated as a white solid after recrystallization from ethanol (200 mg, 71%); $[\alpha]_D^{25}$ +47.4 (*c* 1.14 in H_2O) (Found: C, 46.8; H, 8.1; N, 8.0. $C_7H_{14}ClNO_2$ requires C, 46.80; H, 7.86; N, 7.80%).

Acknowledgements

We thank BP International Ltd. for a BP Research Studentship (to I. A. S. W.) and Roussel Laboratories Ltd. for support (to I. L.).

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Paper 4/00708E
Received 4*th February* 1994
Accepted 24*th February* 1994