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Resolution of *trans*-3-aminocyclohexanol

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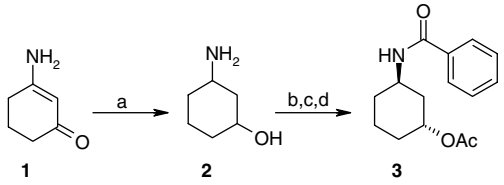
Abstract—(*R*,*R*)- and (*S*,*S*)-*trans*-3-Aminocyclohexanol were prepared via an enzymatic resolution of (±)-*trans*-1-acetoxy-3-benzylamido-cyclohexane with >95% enantiomeric excess.

1. Introduction

Enantiomerically pure *trans*-3-aminocyclohexanols were required during a study of thiadiazoles and oxadiazoles as PDE7 inhibitors.[1] On examination of the literature, there were no reported syntheses of enantiomerically pure 3-aminocyclohexanols and to the best of our knowledge there has been very little chemistry describing this core structure.[2] Herein we report a methodology for obtaining enantiomerically pure (*S*,*S*)- and (*R*,*R*)-3-aminocyclohexanols by selective enzymatic hydrolysis of 1-acetoxy-3-benzylamidocyclohexane. Asymmetric syntheses to access these entities were ruled out at an early stage due to the potential difficulties of controlling the regio- and stereochemistry.

2. Results and discussion

Approaches to access *rac-trans*-3-aminocyclohexanol have already been reported in the literature,[3,4] although a number of these are of limited use for larger scale chemistry. Raney Nickel reduction of 3-aminocyclohex-2-enone **1** looked promising for the synthesis of racemic 3-aminocyclohexanol **2** as described by Greenhill et al.[4] This methodology reportedly gives a mixture of the *cis*- and *trans*-3-aminocyclohexanols in a *cis:trans* ratio of 1:2; we observed the ratio to vary between 1:2 and 1:1 on 0.5 kg scale. The *N*-benzoyl derivative **3** was formed to allow separation of the *cis*/*trans* isomers by crystallization[3] from $CHCl_3$ (Scheme 1).



Scheme 1. Reagents and conditions: (a) RaneyNi, EtOH, 20% aq NaOH, H_2 (10 atm); (b) PhCOCl, NaOH; (c) $CHCl_3$ recrystallization; (d) AcCl, Et_3N, THF.

The desired *trans*-3-aminocyclohexanol was acetylated and the material subjected to enzyme ester hydrolysis. An enzyme screen was carried out at this stage for resolution of **3**, using a ChiroScreen® test kit containing 31 separate enzymes. The rate of conversion for 30 of the enzymes was found to be negligible, apart from Novozyme® 435 (*Candida Antarctica B*), which gave an acceptable rate of conversion and good enantiomeric excess.

Novozyme® 435 (*Candida Antarctica B*) was used to provide the resolved (*R*,*R*)-3-benzylamidocyclohexanol **5** and (*S*,*S*)-3-benzylamidoacetoxycyclohexane **4**. The mixture was then subjected to chromatographic separation on silica gel to obtain the individual isomers (Scheme 2).

$LiAlH_4$ reduction of the amide and hydrolysis of the acetate provided the 3-benzylaminocyclohexanols. Hydrogenation of the benzyl amines using 10% Pd/C 50% wet Degussa paste furnished the individual isomers of 3-aminocyclohexanols **6** and **7** in >95% ee (Scheme 3).

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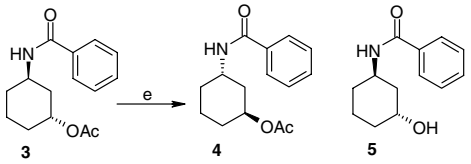
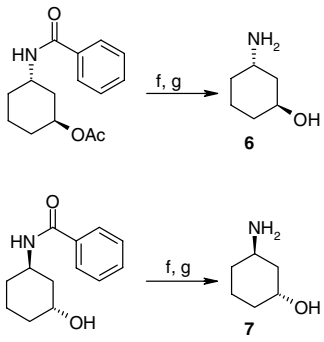


Scheme 2. Reagents and conditions: (e) Novozyme 435, PhMe, EtOH, 120 h.



Scheme 3. Reagents and conditions: (f) $LiAlH_4$, THF; (g) Pd/C (10%), EtOH, H_2 (1 atm).

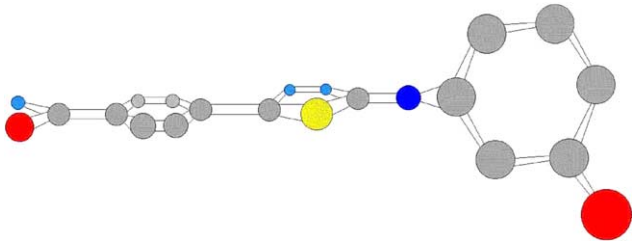
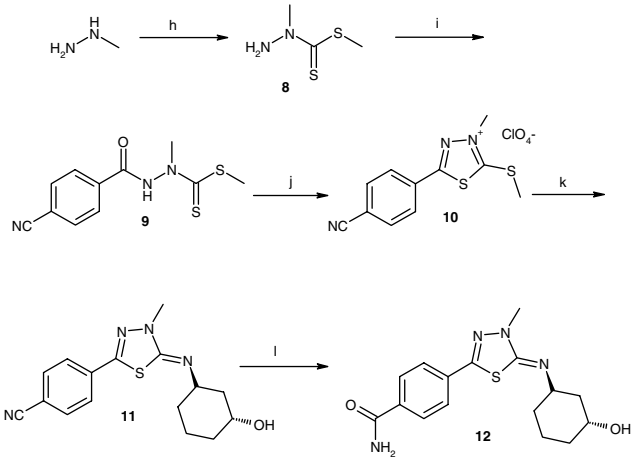


Figure 1.



Scheme 4. Reagents and conditions: (h) KOH, CS_2, MeI; (i) 4-cyanobenzoyl chloride, PhMe; (j) acetic anhydride, $HClO_4$, Et_2O; (k) (*R*,*R*)-3-aminocyclohexanol, Et_3N, EtOH; (l) EtOH, Na_2CO_3, H_2O_2.

The absolute configuration of 3-aminocyclohexanol **7** was determined by X-ray crystallography[5] of the 4-{5-[(1*R*,3*R*)-3-hydroxycyclohexylimino]-4-methyl-4,5-dihydro-[1,3,4]-thiadiazol-2-yl}benzamide[1] derivative **12** (Fig. 1, Scheme 4). The most suitable solvent for the growth of a crystal of this material was EtOH; evaporating the solvent slowly at 19 °C formed needle shaped crystals.

3. Conclusions

The methodology disclosed provides an enzymatic resolution to obtain both enantiomers of 3-aminocyclohexanol with an enantiomeric excess of over 95% and has been used to obtain 60 g of the individual enantiomers. These were then employed in the synthesis of a number of oxadiazole and thiadiazoles as PDE7 inhibitors.[1] The enzyme Novozyme® 435 is commercially available in large quantities.

4. Experimental

^1H and ^{13}C NMR spectra were run on a Bruker FT spectrometer at 360, 400, and 75 MHz, respectively. Mass spectral data was recorded on Waters ZQ2000 single quadrapole. Optical rotations were recorded on a Perkin Elmer polarimeter 141. Enantiomeric excess was determined on the benzamide derivative by chiral HPLC on a Chiracel OD column, 250 mm × 4.6 mm, 5 μm; mobile phase: Heptane+0.1%DEA/propan-2-ol+0.1% DEA(80/20 v/v/v); flow rate:1 mL/min; Injection volume: 20 μL; run time: 12 min; detection: UV at 225 nm; column oven temperature: 20 °C; sample temperature: 20 °C.

4.1. 3-Aminocyclohexanol (1:1 *trans*/*cis* isomers) 2

To a 2 L pressure reactor was charged 3-amino-2-cyclohexen-1-ol (100 g, 0.90 mol), ethanol (700 mL), 20% w/v NaOH (19 mL), and Raney-Nickel (100 g). The reaction was subjected to H_2 (10 bar) at a temperature of 40–55 °C (caution: exothermic reaction). The reaction mixture was filtered, concentrated in vacuo, the crude oil taken up in DCM (1000 mL), dried over magnesium sulfate, and concentrated in vacuo to give 79 g (77%th) of the title compound as a 1:1 mixture of *trans*/*cis* isomers. ^1H NMR (360 MHz, $(CD_3)_2SO$, δ_H) 3.85 (br s, 0.5H), 3.2 (m, 0.5H), 2.9 (m, 0.5H), 2.5 (m, 0.5H), 1.9 (br d, 1H), 1.7 (br d, 1H), 1.65–1.30 (m, 5H), 1.3–0.7 (m, 5H).

4.2. (*rac*)-*trans*-1-(3-Hydroxycyclohexyl)benzamide

A solution of sodium hydroxide (59 g, 1.48 mol) in water (790 mL) was cooled to 0–5 °C and 3-aminocyclohexanol (79 g, 0.68 mol) charged. To this mixture was added, portionwise, benzoyl chloride (160 mL, 1.38 mol) over a period of 20 min while maintaining the temperature at 20 °C. The mixture was stirred for 3 h and extracted with ethyl acetate at ca. 45 °C. The extracts were concentrated in vacuo to give the crude material as an off-white sticky solid. The crude material was crystallized from chloroform (550 mL) and methanol (30 mL). The isolated product was re-crystallized from chloroform (500 mL)/methanol (45 mL) and dried in vacuo to give

25.7 g (17%th) of the desired racemic *trans*-1-(3-hydroxycyclohexyl)benzamide as a white crystalline solid. ^{1}H NMR (360 MHz, $(CD_3)_2SO$, δ_H) 8.14 (d, $J = 8$ Hz, 1H), 7.83 (d, $J = 7$ Hz, 2H), 7.53–7.42 (m, 3H), 4.48 (s, 1H), 4.23 (m, 1H), 4.00 (br s, 1H), 1.79–1.31 (m, 8H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$, δ_C) 166.3, 135.8, 131.7, 128.9, 128.1, 65.6, 44.7, 33.1, 32.9, 20.0.

4.3. (*rac*)-*trans*-1-Acetoxy-3-benzylamidocyclohexane 3

To a stirred suspension of the *trans*-1-(3-hydroxycyclohexyl)benzamide (15 g, 0.68 mol) in THF (500 mL) at 0–5 °C, was charged triethylamine (25.8 mL, 2.75 equiv) and acetyl chloride (9.5 mL, 2.0 equiv) over ca. 5 min (exothermic) while maintaining the temperature below 20 °C. Two further portions (as above) of Et_3N and AcCl were added after 1 and 2 h. The precipitate was filtered and washed with THF (200 mL), the filtrate concentrated in vacuo, and the residue taken up in ethyl acetate (500 mL) and water (500 mL). The phases were separated and the organic phase washed with brine (200 mL), dried over magnesium sulfate, and concentrated in vacuo to give a sticky orange solid. The crude material was slurried in TBME (100 mL) for 30 min at ambient temperature, cooled to <10 °C, and filtered. The filter cake was washed with TBME (2 × 50 mL) and dried in vacuo at 40 °C to give 13.48 g (75%) of the (*rac*)-*trans*-3-benzylamidoacetoxy cyclohexane as a pale orange solid. ^{1}H NMR (360 MHz, $(CD_3)_2SO$, δ_H) 7.78–7.62 (m, 2H), 7.53–7.43 (m, 3H), 6.03 (d, $J = 6$ Hz), 5.18 (br s, 1H), 4.40–4.36 (m, 1H), 2.25–2.05 (m and s, 2H and 3H), 1.85–1.56 (m, 5H), 1.38–1.27 (m, 1H).

4.4. (*S*,*S*)-1-Acetoxy-3-benzylamidocyclohexane 4 and (*R*,*R*)-3-benzylamidocyclohexanol 5

To a suspension of (*rac*)-*trans*-3-benzylamidoacetoxy cyclohexane (13.0 g, 0.05 mol) in toluene (325 mL) were charged Novozym® 435 (19.5 g) and ethanol (37 mL) at 18–22 °C. The mixture was stirred for 120 h, after which the catalyst was filtered through a pad of Celite® and the filter cake washed with ethanol (300 mL). The filtrate was concentrated in vacuo. The acetate and alcohol were separated by flash column chromatography on silica gel (20 wt) [eluent: 1:1 ethyl acetate/heptane to elute the acetate (R_f 0.76) and 100% ethyl acetate to elute the (*R*,*R*)-3*N*-benzylamidocyclohexanol (R_f 0.36)] to give 5.2 g (47.5%) of the alcohol. ^{1}H NMR (360 MHz, $(CD_3)_2SO$, δ_H) 8.14 (d, $J = 8$ Hz, 1H), 7.83 (d, $J = 7$ Hz, 2H), 7.53–7.42 (m, 3H), 4.48 (s, 1H), 4.23 (m, 1H), 4.00 (br s, 1H), 1.79–1.31 (m, 8H); and 5.2 g (40%) of the (*S*),(*S*)-3-benzylamidoacetoxycyclohexane. ^{1}H NMR (360 MHz, $(CD_3)_2SO$, δ_H) 7.78–7.62 (m, 2H), 7.53–7.43 (m, 3H), 6.03 (d, $J = 6$ Hz), 5.18 (br s, 1H), 4.40–4.36 (m, 1H), 2.25–2.05 (m and s, 2H and 3H), 1.85–1.56 (m, 5H), 1.38–1.27 (m, 1H).

4.5. (*S*,*S*)-3-*N*-Benzylaminocyclohexanol

To a suspension of $LiAlH_4$ (2.90 g, 4 equiv) in anhydrous THF (150 mL) was charged (*S*,*S*)-3*N*-benzylamidoacetoxycyclohexane (5 g, 0.19 mol) portionwise. The mixture was heated at reflux for 72 h, cooled and quenched with water (2.90 mL) and 20% aqueous NaOH (2.90 mL). Water (8.7 mL) was added, agitated for 20 min, and filtered. The lithium salts were washed with THF (100 mL) and the solvents removed in vacuo at 40 °C to provide the crude product as a tan oil, which was subjected to chromatography on silica to give (*S*,*S*)-3*N*-benzylaminocyclohexanol (2.61 g, 70%th). ^{1}H NMR (360 MHz, $(CD_3)_2SO$, δ_H) 7.36–7.21 (m, 5H), 4.28 (br s, 1H), 3.89 (br s, 1H), 3.70 (s, 2H), 2.81–2.79 (m, 1H), 1.66–1.63 (m, 2H), 1.52–1.38 (m, 6H), 1.21–1.18 (m, 1H).

4.6. (*S*,*S*)-3-Aminocyclohexanol 6

To a stirred suspension of 10% palladium on carbon (1.25 g) (50% wet Degussa type E101) in ethanol (25 mL) was charged (*S*,*S*)-3*N*-benzylaminocyclohexanol (2.50 g, 0.013 mol) as a solution in ethanol (25 mL) under nitrogen. The reaction vessel was purged with hydrogen and the mixture stirred vigorously under 1 atm of hydrogen for ca. 16 h. The reaction vessel was purged with nitrogen, the catalyst removed by filtration, and washed with ethanol (50 mL, 20 vol) under a blanket of nitrogen. The filtrate was concentrated in vacuo at 40 °C, taken up in chloroform (25 mL), and dried over magnesium sulfate. The filtrate was concentrated in vacuo at 40 °C to give (*S*,*S*)-3-aminocyclohexanol as a colorless solid (1.25 g, 87%). ^{1}H NMR (360 MHz, $(CD_3)_2SO$, δ_H) 4.15 (br s, 1H), 3.19–3.12 (m,1H), 1.89–1.38 (m, 7H, br s, OH and NH_2), 1.21–1.12 (m, 1H); ^{13}C NMR (MHz, $(CDCl_3)$, δ_C) 67.1, 45.9, 43.3, 36.1, 33.4, 30.7, 19.6; $[\alpha]_D^{20} = +7.5$ (*c* 1, CH_3OH); ee (HPLC)[6] 95.46%.

4.7. (*R*,*R*)-3-Benzylaminocyclohexanol

To a suspension of $LiAlH_4$ (2.63 g, 3 equiv) in anhydrous THF (150 mL) was charged (*R*,*R*)-3*N*-benzylamidocyclohexanol (5.0 g, 0.023 mol) portionwise. Once all the substrate was charged, the mixture was heated to reflux for 72 h. The reaction was cooled to 0–5 °C in an ice/water bath and water (2.63 mL) added very carefully to the mixture over ca. 20 min maintaining the temperature below 15 °C. This was followed by 15% sodium hydroxide solution (2.63 mL), again added carefully over 20 min while maintaining the temperature below 15 °C. To this thick mixture was charged water (7.89 mL) and the mixture stirred at 10–20 °C for 15 min. The solids were filtered and washed with THF (100 mL) and the filtrate concentrated in vacuo at 40 °C. The crude material was purified by flash column chromatography on silica gel (20 wt) using 100% ethyl acetate to 8:2 ethyl acetate/methanol to elute the product. The fractions were concentrated at 40 °C to give 2.3 g, 52%th (corrected for residual solvents) of the title compound as a yellow oil. ^{1}H NMR (360 MHz, $(CD_3)_2SO$, δ_H) 7.36–7.21 (m, 5H), 4.28 (br s, 1H), 3.89 (br s, 1H), (s, 2H), 2.81–2.79 (m, 1H), 1.66–1.63 (m, 2H), 1.52–1.38 (m, 6H), 1.21–1.18 (m, 1H).

4.8. (*R*,*R*)-3-Aminocyclohexanol 7

To a stirred suspension of 10% palladium on carbon (1.25 g) (50% wet Degussa type E101) in ethanol (25 mL) was charged (*R*,*R*)-3-benzylaminocyclohexanol (2.50 g, 0.013 mol) as a solution in ethanol (25 mL) under nitrogen. The reaction vessel was purged with hydrogen and the mixture stirred vigorously under 1 atm of hydrogen for ca. 16 h. The reaction vessel was purged with nitrogen, the catalyst removed by filtration, and washed with ethanol (50 mL, 20 vol) under a blanket of nitrogen. The filtrate was concentrated in vacuo at 40 °C, taken up in chloroform (25 mL), and dried over magnesium sulfate. The filtrate was concentrated in vacuo at 40 °C and the resulting solid dried under high vacuum for approximately 3 h to give 1.25 g (87%th) of (*R*,*R*)-3-aminocyclohexanol. ^{1}H NMR (360 MHz, $(CD_3)_2SO$, δ_H) 4.15 (br s, 1H), 3.19–3.12 (m, 1H), 1.89–1.38 (m, 7H and br s, OH and NH_2), 1.21–1.12 (m, 1H); ^{13}C NMR (75 MHz, ($CDCl_3$), δ_C) 67.1, 45.9, 43.3, 36.1, 33.4, 30.7, 19.6; $[\alpha]_D^{20} = -8.5$ (*c* 1, CH_3OH), ee (HPLC)[6] 97.3%.

4.9. *N*-Methyl-hydrazinecarbodithioic acid methyl ester 8

Methylhydrazine (19.43 mL, 370 mmol) was added to a solution of potassium hydroxide (20.7 g, 370 mmol) in 90% aqueous ethanol (130 mL). The mixture was cooled to 5 °C, then carbon disulfide (22.2 mL, 370 mmol) added dropwise with vigorous stirring over 1 h while maintaining the temperature at <70 °C. The resulting yellow solution was diluted with water (300 mL) and then methyl iodide (23.34 mL, 370 mmol) added slowly while the mixture was stirred vigorously. The stirring was continued for 3 h at 10–15 °C, the 2-methyl-(*S*)-methyldithiocarbazate precipitated as white crystals. The precipitate was filtered and washed with a mixture of 1:1 ethanol/petroleum ether to give 2-methyl-(*S*)-methyldithiocarbazate (38 g, 84%th). ^{1}H NMR (400 MHz, $(CD_3)_2SO$, δ_H) 2.32 (s, 3H), 3.60 (s, 3H), 5.55 (s, 2H).

4.10. *N*′-[1-(4-Cyanophenyl)-methanoyl]-*N*-methyl-hydrazinecarbodithioic acid methyl ester 9

4-Cyanobenzoylchloride (3.77 g, 22.77 mmol) was added to a suspension of *N*-methyl-hydrazinecarbodithioic acid methyl ester (3.10 g, 22.77 mmol) and toluene (25 mL). The mixture was stirred and refluxed for 3.5 h and allowed to cool to ambient temperature overnight. The solids were filtered, washed with water and diethyl ether, and dried to give *N*′-[1-(4-cyanophenyl)-methanoyl]-*N*-methyl-hydrazinecarbodithioic acid methyl ester (4.15 g, 68%th). ^{1}H NMR (400 MHz, $(CD_3)_2SO$, δ_H) 2.45 (s, 3H), 3.65 (s, 3H), 8.05 (m, 4H), 11.85 (s, 1H).

4.11. 1,3,4-Thiadiazolium-5-(4-cyanophenyl)-3-methyl-2-(methylthio)perchlorate 10

To a suspension of *N*′-[1-(4-cyanophenyl)-methanoyl]-*N*-methyl-hydrazinecarbodithioic acid methyl ester (4.15 g, 15.64 mmol) in diethyl ether (50 mL) and acetic anhydride (13.3 mL), $HClO_4$ 70% (1.6 mL, 18.76 mmol) was added dropwise at 0 °C and stirred for 30 min at 0 °C. The reaction was stirred for 90 min at ambient temperature, the precipitate separated by filtration and the solid washed with diethyl ether, and air dried to give 1,3,4-thiadiazolium-5-(4-cyanophenyl)-3-methyl-2-(methylthio)perchlorate as a white solid (5.22 g, 96%th). ^{1}H NMR (400 MHz, $(CD_3)_2SO$, δ_H) 3.15 (s, 3H), 4.21 (s, 3H), 8.15 (m, 4H).

4.12. 4-[5-{(1*R*,3*R*)-3-Hydroxycyclohexylimino}-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]benzonitrile 11

To a suspension of 1,3,4-thiadiazolium-5-(4-cyanophenyl)-3-methyl-2-(methylthio)perchlorate (1.22 g, 3.5 mmol) in ethanol (80 mL), (1*R*,3*R*)-3-aminocyclohexanol (0.485 mg, 4.2 mmol) and triethylamine (4.2 mmol, 587 μL) were added and the mixture stirred at reflux for 4 h. The mixture was concentrated in vacuo and the residue purified by chromatography on silica gel eluting with a gradient of cyclohexane containing 0–60% ethyl acetate to give 4-[5-{(1*R*,3*R*)-3-hydroxycyclohexylimino}-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]benzonitrile (120 mg, 11%th). ^{1}H NMR (400 MHz, $(CD_3)_2SO$, δ_H) 1.35–1.50 (m, 2H), 1.50–1.70 (m, 6H), 3.04–3.12 (m, 1H), 3.54 (s, 3H), 3.88–3.96 (m, 1H), 4.44 (d, 1H), 7.80 (dd, 2H), 7.94 (dd, 2H).

4.13. 4-[5-{(1*R*,3*R*)-3-Hydroxycyclohexylimino}-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide 12

To a suspension of 4-[5-{(1*R*,3*R*)-3-hydroxycyclohexylimino}-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile (150 mg, 0.477 mmol) in ethanol (17 mL), a solution of sodium carbonate (3 M, 1.7 mL, 5.1 mmol) and a solution of H_2O_2 (30% in H_2O) (1.4 mL) were added and the mixture stirred overnight at ambient temperature. The reaction mixture was poured onto water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated in vacuo and the resulting solid stirred in water for several hours, filtered, and dried in vacuo to afford 4-[5-{(1*R*,3*R*)-3-hydroxycyclohexylimino}-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide (49 mg, 31%). ^{1}H NMR (400 MHz, $(CD_3)_2SO$, δ_H) 1.30–1.70 (m, 8H), 3.10 (s, 1H), 3.52 (s, 3H), 3.93 (s, 1H), 4.42 (d, 1H), 7.43 (s, 1H), 7.70 (dd, 2H), 7.96 (dd, 2H), 8.05 (s, 1H); MS (*m*/*z*), M+1 = 333. Crystallization was carried out by dissolution of **12** in the minimum amount of EtOH, followed by slow evaporation of the solvent at 19 °C to provide single needle shaped crystals suitable for X-ray crystallography.

Acknowledgements

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5. X-ray crystallographic analysis of **12** was carried out by Laboryx, Le Vernay, 74500 Bernex, France. CCDC 233442 contains the supplementary crystallography data for this paper. The data can be obtained via www.ccdc.cam.ac.uk/conts/retrieving.html. Compound **12**: triclinic P1 $a = 7.1745(14)$; $b = 9.4432(19)$; $c = 12.0085(24)$; $\alpha = 80.283(30)$; $\beta = 80.810(30)$; $\gamma = 88.174(30)$; $V = 791.60\ \text{Å}^3$. Determination of the absolute configuration is based on the refinement of the Flack parameters.
6. To confirm the ee, a 50 mg sample of the 3-aminocyclohexanol was derivatized to the benzamide using the conditions in stage 2, to give the crude benzamide as an off white solid (^{1}H NMR analysis indicated this crude product was a mixture of the desired benzamide and benzoic acid). This crude material was used directly for analysis (chiral HPLC).