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Synthesis of enantiopure *cis*- and *trans*-2-aminocyclohexane-1-carboxylic acids from octahydroquinazolin-4-ones

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Abstract—The chemoselective and diastereoselective hydrogenation of 2,3-dihydro-3-[(*S*)-α-methylbenzyl]-4-quinazolinone **2** affords octahydroquinazolinones *cis*-**3** and *cis*-**4**. Epimerization of *cis*-**3** and *cis*-**4** using *t*-BuO^-K^+ produces *trans*-**5** and *trans*-**6**, respectively. Hydrolysis with HCl of these octahydroquinazolinones leads to the free, enantiomerically pure, *cis*- and *trans*-2-aminocyclohexane-1-carboxylic acids **7**–**10**.

1. Introduction

Enantiomerically pure cyclic β-amino acids have been of considerable interest owing to their potential use as therapeutic agents and for their role as structure-forming elements in β-peptides, which possess an ability to adopt stable secondary structures such as oligomers.[1] For example, *trans*-aminocyclohexanecarboxylic acid has recently been shown by Gellman et al. to form 14- and 12 helices that are generally more rigid and stable than those comprised of linear α- and β-amino acids.[2–7] Furthermore, modification of the carbocyclic ring of these monomeric units to include additional functional groups has led to foldamers with enhanced solubility in aqueous media.[8,9]

Given the significance of cyclic β-amino acids, it is not surprising that their synthesis has become an important and challenging endeavour for organic chemists. Numerous methodologies have appeared in the literature, with the subject being extensively reviewed.[10] The most widely used techniques employ diastereo- and enantioselective syntheses,[11] chemoselective resolution[12] and enzymatic separations.[13] Therefore, the goal herein is to provide a new synthesis of all four isomers of 2-amino cyclohexanecarboxylic acid, through the use of 2-aminobenzamide **1** as the chiral block for assembly of quinazolinone **2**. It is intended to complement methods already reported.

Herein, we report a versatile method for the enantiomerically pure preparation of the *cis*- and *trans*-2-aminocyclohexane-1-carboxylic acids **7**–**10**, from 2,3-dihydro-3-[(*S*)-α-methylbenzyl]-4-quinazolinone **2**. The key to our strategy is the diastereoselective synthesis of octahydroquinazolinones *cis*-**3** and **4**, which can also be epimerized under basic conditions to produce stereoisomers *trans*-**5** and **6**, respectively (Fig. 1).

2. Results and discussion

2.1. Synthesis of 3,4-dihydro-3-[(*S*)-α-methylbenzyl]-4-quinazolinone 2

The 2-aminobenzamide **1** was obtained through treatment of isatoic anhydride with (*S*)-α-methylbenzylamine (Scheme 1).[14] Subsequently, the cyclocondensation with triethyl orthoformate and *p*-TsOH in toluene yielded quinazolinone **2** in 93% overall yield.

2.2. Synthesis of octahydroquinazolinones *cis*-3, *cis*-4 and *trans*-5

Hydrogenation of **2** with PtO_2 catalyst at 60 lb for 30 min in AcOH and catalytic H_2SO_4 gave the target compounds **3**–**5**. Spectroscopic analysis by ^1H NMR

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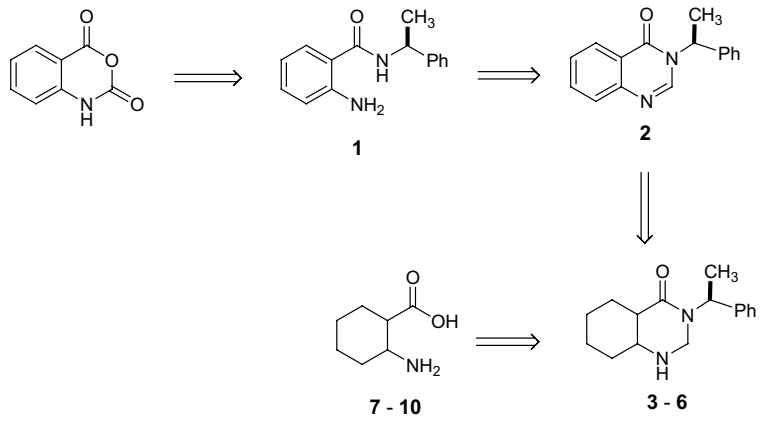
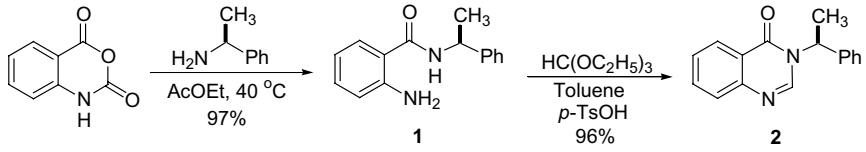


Figure 1. Retrosynthetic analysis.



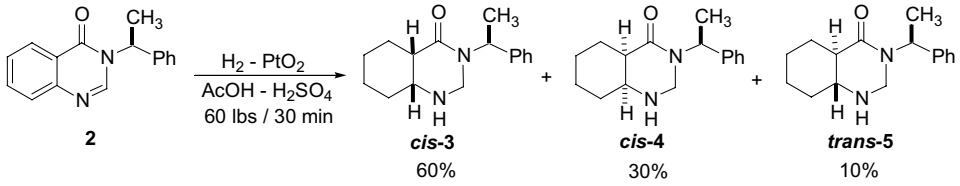
Scheme 1.

showed a mixture of diastereoisomers *cis*-**3**, *cis*-**4** and *trans*-**5** in a ratio of 60:30:10, respectively (Scheme 2).

The stereochemistry of each compound was confirmed by X-ray. The major stereoisomer was identified as *cis*-**3** (Fig. 2) with the second product corresponding to *cis*-**4**. Finally, it is important to point out that in this hydrogenation reaction we observed another stereoisomer with low yield, which has been assigned as *trans*-**5** by X-ray (vide infra).

The hydrogenation reaction was chemoselective: no reduction of the phenyl group in the chiral auxiliary at *N*-3 was observed.

With these intermediates in hand, we investigated the epimerization reaction of the *cis*-diastereoisomers in the formation of the *trans*-octahydroquinazolinones **5** and **6**, (Scheme 3). From the crystal structure of the product derived from the epimerization of *cis*-**3**, the stereochemistry is deduced as *trans*-**5** (Fig. 3).



Scheme 2.

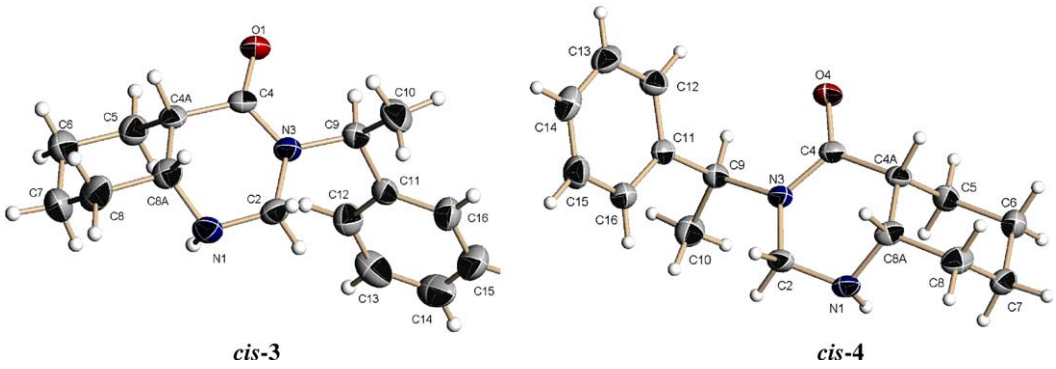
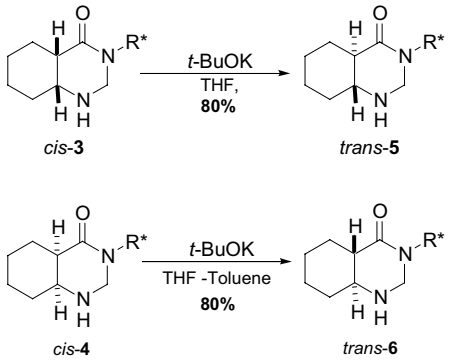


Figure 2. X-ray structures of *cis*-**3** and *cis*-**4**.



Scheme 3.

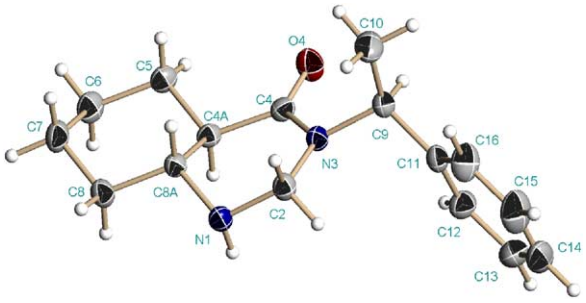


Figure 3. X-ray structure of octahydroquinazolinone *trans*-**5**.

This result, with the specific rotation, permits the assignment of the relative configuration of the product, which was obtained in lower quantity in the hydrogenation reaction, as *trans*-**5**. The stereochemistry of *trans*-**6** was determined by chemical correlation with the free β-amino acid.

2.3. Hydrolysis of the octahydroquinazolinones 3–6 to produce the *cis*- and *trans*-2-aminocyclohexane-1-carboxylic acids 7–10

The final step of the overall conversion of isatoic anhydrides to β-amino acids, the hydrolysis of quinazolinones **3**–**6**, was achieved by heating to 115–120 °C with 6 M HCl in a sealed tube (Scheme 4). The free amino acids **7**–**10** were purified by chromatography on an ion-exchange column (Dowex® 50WX8-200); the yields were ca. 75%.

The specific rotations, melting points and the ^{1}H and ^{13}C NMR spectra of compounds **7**–**10** were found to be essentially identical with those values already present in the literature.

3. Conclusions

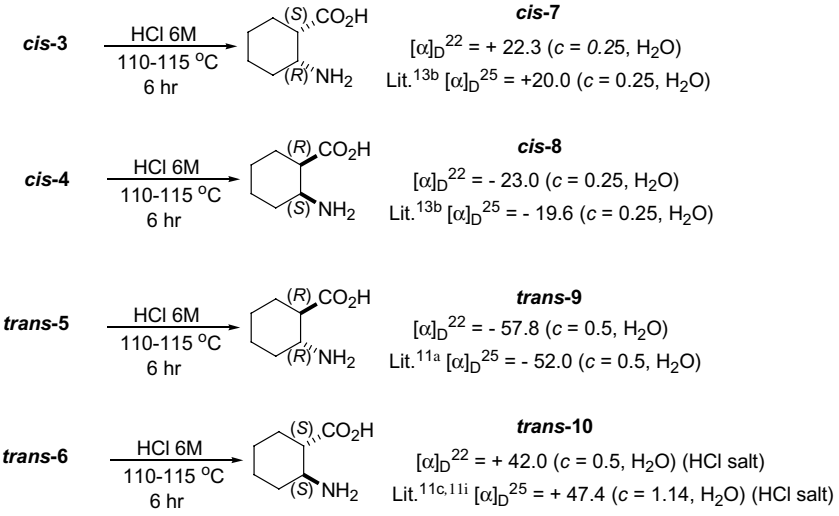
We have reported a method for the preparation of both *cis*- and *trans*-2-aminocyclohexane-1-carboxylic acids in enantiomerically pure form from octahydroquinazolinones. This method would be suitable for preparing a variety of structural analogues.

4. Experimental

4.1. General

For a description of the general experimental data, see Ref. 15. Microanalyses were performed in Elementar Vario EL III. Optical rotations: 10 cm, 1 mL cell, Perkin–Elmer-341 polarimeter.

4.1.1. 2-Amino-*N*-[(*S*)-α-methylbenzyl]-benzamide 1. 1.1 equiv of the (*S*)-α-methylbenzylamine (0.9 mL, 7.0 mmol) was added to a suspension of isatoic anhydride (1 equiv, 1.0 g, 6.2 mmol) in ethyl acetate (15 mL, 0.62 M). The reaction mixture was warmed to 35–40 °C for 40 min. The solution was then concentrated under reduced pressure. The crude product was purified by FC (hexane–ethyl acetate, 70:30 → 50:50) to afford 1.44 g (97% yield) of **1**, as a white solid: mp 136–138 °C; $[\alpha]_D^{24} = +110.9$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (3H, d, $J = 7.0$ Hz), 5.28 (1H, dq, $J_1 = J_2 = 7.0$ Hz), 6.29 (1H, d, $J = 6.2$ Hz), 6.62 (1H, d, $J_{ortho} = 7.3$ Hz), 6.66 (1H, t, $J_{ortho} = 8.4$ Hz), 7.20 (1H, td, $J_{meta} = 1.5$ Hz, $J_{ortho} = 7.7$ Hz), 7.26–7.40 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ



Scheme 4.

22.0, 48.9, 116.6, 116.6, 117.4, 126.1, 127.1, 127.4, 128.8, 132.2, 143.4, 148.8, 168.4. Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.22; H, 6.78; N, 11.32. Found: C, 74.97; H, 6.71; N, 11.66.

4.1.2. 3,4-Dihydro-3-[(*S*)-α-methylbenzyl]-4-quinazolinone 2. A solution of the aminobenzamide **1** (1 equiv, 1.0 g, 4.16 mmol) in toluene (20 mL) was treated with triethyl orthoformate (1.1 equiv, 0.7 mL, 4.58 mmol), *p*-toluenesulfonic acid monohydrate (0.1 g) and the reaction mixture heated to 40 °C for 2 h. The organic layer was concentrated under reduced pressure. The crude product was purified by FC (hexane–ethyl acetate 70:30 → 50:50) to produce 1.01 g (96% yield) of **2**, as an oil: $[\alpha]_D^{24} = -277.0$ (*c* 0.50, MeOH), ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.85 (3H, d, $J = 7.0$ Hz), 6.38 (1H, q, $J = 6.8$ Hz), 7.38 (5H, m), 7.48 (1H, dd, $J_{meta} = 1.8$ Hz, $J_{ortho} = 7.6$ Hz), 7.65–7.80 (2H, m), 7.94 (1H, s), 8.36 (1H, dd, $J_{meta} = 1.6$ Hz, $J_{ortho} = 8.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.3, 51.9, 122.0, 127.2, 127.4, 127.5, 127.5, 128.5, 129.2, 134.4, 139.6, 144.6, 147.7, 161.0. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.45; H, 5.70; N, 10.97.

4.2. General procedure for the hydrogenation of quinazolinone 2

Quinazolinone **2** (1.0 g, 4.0 mmol), 10 mL of acetic acid, two drops of sulfuric acid, 0.02 g of PtO_2 catalyst and activated charcoal (0.8 g) were combined, and the mixture shaken at room temperature in a Parr hydrogenator for 30 min under 60 psi of hydrogen. The catalyst was filtered through Celite and the filtrate neutralized with NaOH 30% aq until it reached pH 10–12. The resulting cloudy, aqueous solution, was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed to obtain a pale yellow oil. Octahydroquinazolinones **3**–**5** were purified by FC [hexane/ethyl acetate/isopropyl alcohol (6:3.6:0.4)].

4.2.1. (4a*S*,8a*R*)-3-[(*S*)-α-Methylbenzyl]-1,2,4a,5,6,7,8,8a-octahydroquinazolin-4-one 3. 0.558 g (60% yield) as a white crystals, mp 113–115 °C; $[\alpha]_D^{24} = -112.8$ (*c* 1.0, MeOH), ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32–1.40 (2H, m), 1.51 (3H, d, $J = 7.6$ Hz), 1.54–1.77 (6H, m), 1.90–1.97 (1H, m), 2.44 (1H, dt, $J = J = 4.4$ Hz, $J = 14.8$ Hz), 3.17 (1H, dd, $J = J = 4.4$ Hz), 3.83 (1H, d, $J = 11.6$ Hz), 4.17 (1H, d, $J = 12.0$ Hz), 6.06 (1H, q, $J = 7.2$ Hz), 7.25–7.37 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.8, 21.6, 24.7, 26.3, 30.3, 43.1, 48.4, 51.7, 56.9, 127.3, 127.5, 128.7, 140.7, 171.6. Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.42; H, 8.53; N, 10.85. Found: C, 74.51; H, 8.64; N, 10.71. X-ray crystallographic structure in Figure 2.[16]

4.2.2. (4a*R*,8a*S*)-3-[(*S*)-α-Methylbenzyl]-1,2,4a,5,6,7,8,-8a-octahydroquinazolin-4-one 4. 0.279 g (30% yield) as a white crystals, mp 128–130 °C; $[\alpha]_D^{24} = -126.0$ (*c* 1.0, MeOH), ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44–1.48 (2H, m), 1.53 (3H, d, $J = 7.2$ Hz), 1.61–1.64 (6H, m), 1.82–1.86 (1H, m), 2.46 (1H, dt, $J = J = 4.8$ Hz, $J = 13.6$ Hz), 3.09 (1H, dd, $J = J = 4.4$ Hz), 3.75 (1H, d, $J = 12.0$ Hz), 4.12 (1H, d, $J = 12.0$ Hz), 6.06 (1H, c, $J = 7.2$ Hz), 7.20–7.40 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.0, 22.3, 24.4, 26.1, 29.9, 43.3, 48.8, 51.6, 56.8, 127.2, 127.5, 128.6, 140.1, 171.1. Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.42; H, 8.53; N, 10.85. Found: C, 73.86; H, 8.56; N, 10.77. X-ray crystallographic structure in Figure 2.[16]

4.2.3. (4a*R*,8a*R*)-3-[(*S*)-α-Methylbenzyl]-1,2,4a,5,6,7,8,8a-octahydroquinazolin-4-one 5. 0.093 g (10% yield) as a white crystals, mp 107–109 °C; $[\alpha]_D^{24} = -83.7$ (*c* 1.0, MeOH); ^{1}H NMR (200 MHz $CDCl_3$) δ 1.09–1.33 (5H, m), 1.52 (3H, d, $J = 7.2$ Hz), 1.79–1.88 (3H, m), 1.93–1.96 (1H, m), 2.46–2.49 (1H, m), 2.57 (1H, ddd, $J = 3.6$ Hz, $J = J = 11.2$ Hz), 3.87 (1H, d, $J = 11.2$ Hz), 4.25 (1H, d, $J = 11.6$ Hz), 6.07 (1H, q, $J = 7.6$ Hz), 7.23–7.36 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.0, 25.5, 26.3, 26.5, 33.9, 49.0, 49.3, 57.5, 56.7, 127.3, 127.4, 128.4, 140.7, 170.1. Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.42; H, 8.53; N, 10.85. Found: C, 74.00; H, 8.60; N, 10.54. X-ray crystallographic structure in Figure 3.[16]

4.3. General procedure for epimerization of *cis*-octahydroquinazolinones

A solution of *cis*-octahydroquinazolinone (0.2 g, 0.78 mmol) in 10 mL anhydrous THF was treated with *t*-BuOK (0.087 g, 0.78 mmol) and heated at reflux for 6 h. The mixture was then evaporated to afford the crude product. The residue was purified by FC (hexane/ethyl acetate/isopropyl alcohol 6:3.6:0.4).

4.3.1. (4a*R*,8a*R*)-3-[(*S*)-α-Methylbenzyl]-1,2,4a,5,6,7,8,8a-octahydroquinazolin-4-one 5. 0.16 g (80% yield) as white crystals. The spectroscopy data were found to be identical with those already presented.

4.3.2. (4a*S*,8a*S*)-3-[(*S*)-α-Methylbenzyl]-1,2,4a,5,6,7,8,8a-octahydroquinazolin-4-one 6. 0.16 g (80% yield) as white crystals, mp 128–130 °C; $[\alpha]_D^{24} = -87.0$ (*c* 1.0, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10–1.29 (4H, m), 1.52 (3H, d, $J = 7.2$ Hz), 1.77–1.92 (4H, m), 1.77–1.92 (1H, m), 2.42–2.49(1H, m), 2.42–2.49 (1H, m), 3.78 (1H, d, $J = 12.0$ Hz), 4.10 (1H, d, $J = 12.0$ Hz), 6.03 (1H, q, $J = 7.2$ Hz), 7.24–7.35 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.0, 25.4, 26.1, 26.6, 34.1, 49.0, 49.0, 57.0, 57.7, 127.4, 127.4, 128.6, 140.1, 170.1. Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.42; H, 8.53; N, 10.85. Found: C, 74.23; H, 8.56; N, 10.76.

4.4. General procedure of the hydrolysis of the *cis*- and *trans*-octahydroquinazolinones

A suspension of 0.1 g (0.39 mmol) of the adduct in 10 mL of 6 M HCl was heated in a sealed ampoule to 110–115 °C for 6 h. The solution was then allowed to cool to ambient temperature. The residue was evaporated at reduced pressure, and treated with a 10% solution of NaOH (pH $\geqslant$10). The aqueous phase was extracted with three 10 mL portions of CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and evaporated to give the crude chiral auxiliary [(*S*)-α-methylbenzylamine]. The aqueous phase was then treated with a

10% solution of HCl until reaching pH $\leqslant 2$. The solution was evaporated at reduced pressure to afford the amino acid hydrochloride, which was absorbed on an acidic ion-exchange resin (Dowex® 50WX8-200). The resin was washed with distilled water until the washings were of neutral pH and then the free amino acid diluted with 1.5 M aqueous NH_4OH. Evaporation afforded the crystalline β-amino acid, which was dried under high vacuum at 50 °C. The resulting solid was recrystallized with acetone/water.

4.4.1. (1*S*,2*R*)-(+)-*cis*-2-Aminocyclohexane-1-carboxylic acid 7. 0.041 g (75% yield) as a colourless solid, mp 217–220 °C (lit.[11h] 220–223 °C); $[\alpha]_D^{24} = +22.0$ (*c* 0.25, H_2O) lit.[13b] $[\alpha]_D^{25} = +20$ (*c* 0.25, H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 1.31–1.86 (8H, m), 2.54 (1H, dt, $J = J = 4.4$ Hz, $J = 7.2$ Hz), 3.37 (1H, dt, $J = J = 4.8$ Hz, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 22.8, 26.1, 27.8, 44.2, 50.0, 181.3.

4.4.2. (1*R*,2*S*)-(−)-*cis*-2-Aminocyclohexane-1-carboxylic acid 8. 0.040 g (73% yield) as a colourless solid, $[\alpha]_D^{24} = -23.0$ (*c* 0.25, H_2O). lit.[13b] $[\alpha]_D^{25} = -19.6$ (*c* 0.25, H_2O).

4.4.3. (1*R*,2*R*)-(−)-*trans*-2-Aminocyclohexane-1-carboxylic acid 9. 0.043 g (76% yield) as a colourless solid, mp 234–235 °C (lit.[12b] 239–240 °C); $[\alpha]_D^{24} = -57.8$ (*c* 0.5, H_2O) lit.[12b] $[\alpha]_D^{25} = -52$ (*c* 0.53, H_2O), ^1H NMR ($CDCl_3$, 400 MHz): δ 1.16–2.05 (3H, m), 2.15 (1H, t, $J = J = 11.4$ Hz,), 3.37 (1H, ddd, $J = 3.8$ Hz, $J = J = 11.4$ Hz), ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.2, 24.9, 29.5, 29.9, 49.1, 52.5, 181.0.

4.4.4. (1*S*,2*S*)-(+)-*trans*-2-Aminocyclohexane-1-carboxylic acid hydrochloride 10. The solid obtained according to general procedure, was treated with a solution of MeOH and HCl gas (10 mL) for 30 min. The residue obtained upon evaporation of the solvent was recrystallized (acetone:water) to yield a colourless solid (0.05 g, 69%): mp 202–204 °C (lit.[11c] 202–206 °C); $[\alpha]_D^{24} = +42.0$ (*c* 0.5, H_2O) (HCl salt) lit.[11c,i] $[\alpha]_D^{25} = +47.4$ (*c* 1.14, H_2O) (HCl salt).

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