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An improved synthesis of (1*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino] cyclohexanecarboxylic acid

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ABSTRACT

An improved synthesis of (1*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]cyclohexanecarboxylic acid from 3-aminobenzoic acid is described utilising milder and more selective conditions. Both a classical salt resolution and an enzymatic approach have been shown to give the desired compound in high selectivity.

1. Introduction

Asymmetric synthesis has long been at the forefront of organic chemistry and as such chiral building blocks are indispensable for the synthesis of biologically active compounds.

Herein we describe an improved synthesis of (1*R*,3*S*)-3-amino-cyclohexancarboxylic acid **5**. Several syntheses of this compound have already been reported,[1–5] however, we required a shorter, scalable route to the title compound.

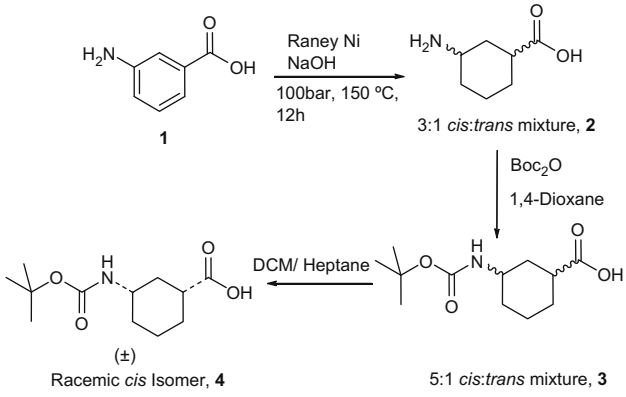
2. Results and discussion

The first generation route which was used to prepare racemic *cis*-3-[(*tert*-butoxycarbonyl)amino]cyclohexane carboxylic acid **4** is shown in Scheme 1.

This follows the route described in the literature[4] where 3-aminobenzoic acid **1** is hydrogenated over Raney nickel at high temperature and pressure. The resulting cycloalkane **2** is obtained as a 3:1 mixture of *cis:trans* isomers which upgrades to a 5:1 mixture **3** on addition of the BOC group. Recrystallisation from DCM and *n*-heptane afforded the racemic *cis* diastereomer **4**.

Whilst this route was able to provide adequate quantities of racemic *cis*-3-[(*tert*-butoxycarbonyl)amino]cyclohexane carboxylic acid **4** there are some drawbacks. Firstly, the Raney nickel reduction conditions were unsuitable for the large quantities we required, and also the ratio of *cis*:*trans* isomers is only 3:1.

Thus milder, more selective hydrogenation conditions were sought. Scheme 2 shows the modified route used, where hydrogenation using rhodium on carbon improves the *cis*:*trans* isomer ratio and crucially proceeds at much lower temperature and pressure.



Scheme 1. Original route used to make racemic *cis*-3-[(*tert*-butoxycarbonyl)amino] cyclohexanecarboxylic acid.

Addition of the BOC group and recrystallisation from DCM/*n*-heptane gave exclusively the *cis* isomer **4**. Although the same chiral amine, namely, (*R*)-1-phenylethylamine was used for the resolution, we used an alternative solvent system of ethanol/heptane which avoided the more hazardous chloroform which had been used previously.

Asymmetric synthesis of the title compound was also considered following the work by Corey[6] on Oseltamivir (Tamiflu). It was envisaged that this elegant and high yielding route could be intercepted at the unsaturated lactam **13** to give the compound we desired in high yield and enantioselectivity, Scheme 3 below shows the proposed route.

However, after initial synthetic investigation it was considered more cost and time effective to prepare the title compound using the resolution route shown in Scheme 2.

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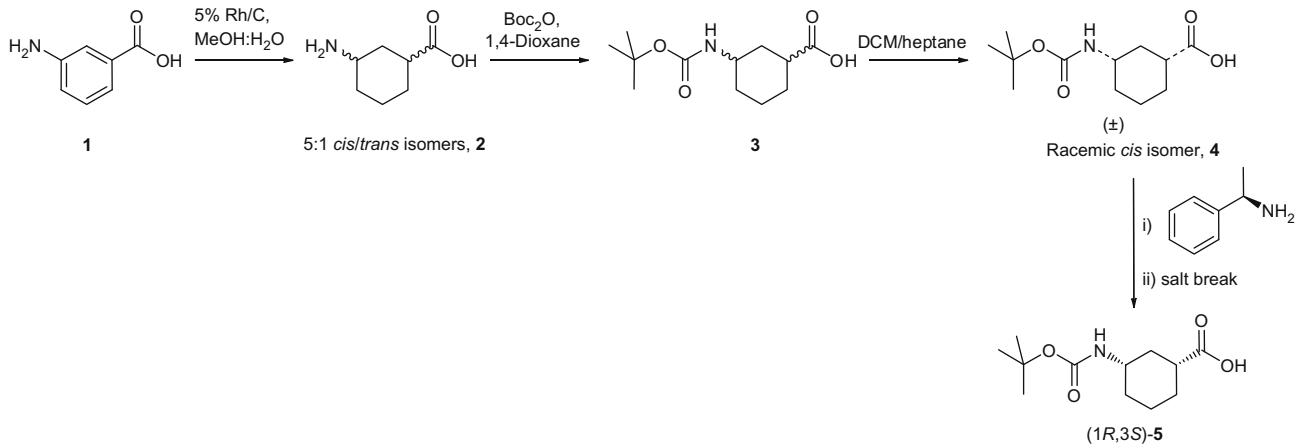
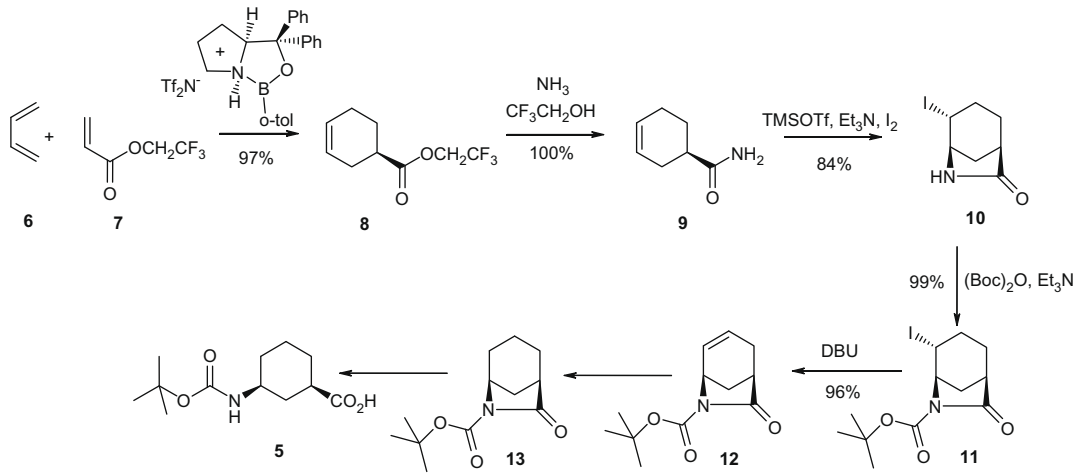
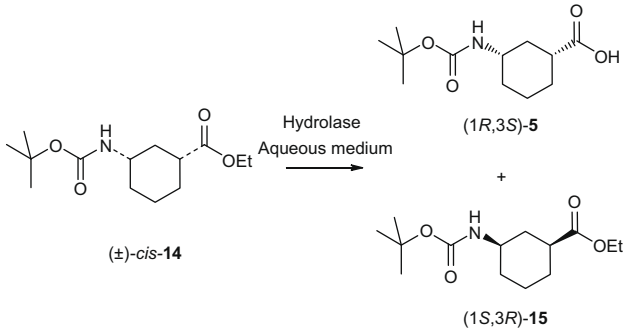


Scheme 2. Modified route used to prepare racemic *cis*-3-[(*tert*-butoxycarbonyl)amino]cyclohexanecarboxylic acid.



Scheme 3. Proposed enantioselective route.



Scheme 4. Enzymatic resolution approach.

3. Enzymatic approach

An alternative resolution approach employing a hydrolase enzyme to selectively convert one stereoisomer of racemic ethyl 3-[(*tert*-butoxycarbonyl)amino]cyclohexane-carboxylic ester **14** to enantiomerically enriched *cis*-(1*R*,3*S*)-acid **5** and unreacted *cis*-(1*S*,3*R*)-ester **15** was envisaged (Scheme 4).

A set of 95 commercially available hydrolases were screened to identify the one most suitable for kinetic resolution of ester **14** employing a high-throughput screening protocol as described by Yasbeck et al.[7] Four of the hydrolases appeared to exhibit highly stereoselective hydrolysis. *Candida antarctica* lipase B (Lipozyme® CALB L), *Pseudomonas cepacia* lipase (Lipase PS 'Amano' SD) and

Table 1
Reactions were conducted at pH 7.0 (90% 0.1 M potassium phosphate buffer with 10% isopropanol co-solvent), 2 mg/mL substrate, 4 mg/mL enzyme, 30 °C. The reactions were allowed to proceed for 72 h and then quenched and analysed by hplc

Entry	Enzyme	Conv (%)	(1*R*,3*S*) Acid **5** ee (%)	(1*S*,3*R*) Ester **15** ee (%)	*E*[a]
1	No enzyme	0			
2	*Candida antartica* Lipase B (Lipozyme® CALB L)	50[b]	96	97	198
3	*Pseudomonas cepacia* lipase (PS 'Amano' SD)	43	92	80	62
4	*Thermomyces lanuginosus* lipase (Lipozyme® TL 100 L)	39	91	58	38
5	Cholesterol esterase from *Candida cylindracea* (Roche)	50	>99 (1*S*,3*R*)	>99 (1*R*,3*S*)	>200

[a] Enantiomeric ratio, *E*, calculated from substrate and product enantiomeric excess by the method of Rakels et al.[8]
[b] Unidentified hplc peak observed of 5.5% of the total hplc area.

Thermomyces lanuginosus lipase (Lipozyme® TL 100L) were selective for the desired *cis*-(1*R*,3*S*)-stereoisomer and cholesterol esterase from *Candida cylindracea* (Roche) was selective for the undesired *cis*-(1*S*,3*R*)-stereoisomer, leaving unreacted *cis*-(1*R*,3*S*)-ester. Enzymatic kinetic resolutions employing the four hydrolases were repeated in 1 mg-scale microreactions (Table 1). The results confirmed this enzymatic approach to be viable with cholesterol esterase from *Candida cylindracea* exhibiting the highest stereoselectivity (Table 1, entry 5, >99% substrate ee and product ee at 50% conversion).

4. Conclusion

A simple, efficient and reliable procedure has been found for the synthesis of 3-[(*tert*-butoxycarbonyl)amino]-cyclohexanecarboxylic acid. In addition to the salt resolution using (*R*)-1-phenylethylamine, a set of four hydrolases have been identified and shown to resolve the racemic *cis*-isomer by the stereoselective hydrolysis of racemic ethyl 3-[(*tert*-butoxycarbonyl)amino]cyclohexane-carboxylic ester.

5. Experimental

5.1. 3-Aminocyclohexanecarboxylic acid, 2 (5:1 mixture)

At first, 3-aminobenzoic acid **1** (30 g, 0.22 mol), methanol (570 mL) and water (30 mL) were charged to a suitable-sized hydrogenation vessel. Rhodium on carbon (5%, Type 20A, 6 g) was charged and the resulting mixture was hydrogenated at 300 PSi and 70 °C. The hydrogen uptake was monitored and the reaction was deemed complete after 3 h at which point water (210 mL) was charged to the reaction slurry to solubilise the product. The reaction mixture was filtered through a plug of Arbocel® and the residue was washed with methanol (90 mL). The filtrate was concentrated to dryness under reduced pressure to leave a white solid residue. The solid was granulated in MeOH (150 mL) for 1 h at room temperature before being isolated by filtration and dried to give the title compound as a white solid (22.6 g, 72% yield).^{1}H NMR ($CDOD_3$) as sodium salt: 0.9–1.4 (m, 3H), 1.4–1.6 (m, 1H), 1.7–1.9 (m, 3H), 2.0–2.2 (m, 2H), 2.5–2.6 (m, 1H).

5.2. 3-[(*tert*-Butoxycarbonyl)amino]cyclohexane carboxylic acid 3

At first, 3-aminocyclohexanecarboxylic acid **2** (5:1 mixture, 22.4 g, 0.16 mol), 1,4-dioxane (225 mL) and water (225 mL) were charged to a 500 mL three-necked flask. Diisopropylethylamine (82 mL, 0.47 mol, 3.0 equiv) was added to the resulting mixture followed by a portionwise addition of di-*tert*-butyl dicarbonate (39.7 g, 0.18 mol, 1.15 equiv). The reaction mixture was stirred at room temperature for 16 h and then concentrated under reduced pressure to remove 1,4-dioxane. Dichloromethane (225 mL) was charged to the residue and the mixture was stirred for 10 min. The organic phase was removed and the aqueous phase was acidified to pH 3 using 20% w/w citric acid solution. The acidic aqueous layer was extracted with dichloromethane (2 × 200 mL). The organic phases were combined, washed with water (100 mL) and dried over $MgSO_4$. Filtration and concentration to dryness afforded the crude product as a sticky solid. The residue was granulated in *n*-heptane (180 mL) for 1 h at room temperature before being isolated by filtration. The filter cake was washed with *n*-heptane (2 × 40 mL) and dried in vacuum oven at 45 °C for 16 h to give the title compound as a white solid (26.34 g, 69%). Analysis of the isolated product by ^{1}H NMR confirmed the presence of the unwanted *trans* isomer.

5.3. Purification to give pure *cis*-isomer 4

At first, 3-[(*tert*-butoxycarbonyl)amino]cyclohexanecarboxylic acid **3** (26 g) and dichloromethane (130 mL) were charged to the reaction vessel giving a clear solution. *n*-Heptane (130 mL) was charged slowly at room temperature and the resulting slurry was granulated for 2–3 h. The mixture was filtered and the cake was washed with *n*-heptane (2 × 20 mL) and dried in vacuum oven at 45 °C for 16 h to afford the title compound as a white solid (16.2 g, 42% yield). ^{1}H NMR (DMSO-d_6) 1–1.3 (m, 5H), 1.3–1.4 (s, 9H), 1.6–1.8 (m, 3H), 1.9–2.0 (m, 1H), 2.1–2.3 (m, 1H), 6.6–6.8 (s, 1H), 11.8–12.1 (s, 1H v broad).

5.4. (1*R*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]cyclohexane-carboxylic acid. (*R*)-1-Phenylethylamine salt

Racemic *cis* 3-[(*tert*-butoxycarbonyl)amino]cyclohexane carboxylic acid **4** (0.5 g, 2.0 mmol) and ethanol (2.5 mL) were charged to the reaction vessel and stirred at room temperature until a solution obtained. (*R*)-1-Phenylethylamine (0.125 g, 1.0 mmol, 0.5 equiv) was charged and the resulting precipitate was stirred at 70 °C until a full solution was obtained which was then allowed cool to ambient temperature and stirred for 16 h. The product was isolated by filtration, washed with *n*-heptane (2 × 5 mL) and dried under vacuum for 16 h at 45 °C to give the title compound as a white solid (0.186 g, 25% yield). ^{1}H NMR (DMSO-d_6) 1.0–1.2 (m, 4H), 1.2–1.3 (m, 1H), 1.3 (d, 3H), 1.4 (s, 9H), 1.6–1.7 (d, 2H), 1.8 (d, 1H), 1.9 (d, 1H), 2.2 (t, 1H), 4.0 (m, 1H), 6.7 (d, 1H), 7.2 (m, 1H), 7.3 (m, 2H), 7.4 (m, 2H).

5.5. (1*R*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]cyclohexane carboxylic acid 5

(1*R*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]cyclohexane carboxylic acid. (*R*)-1-Phenylethylamine salt (45 mg) was suspended in ethyl acetate (10 mL) and washed with 0.1 M aqueous hydrochloric acid (2 × 5 mL). The organic layer was separated, dried over magnesium sulfate, filtered and evaporated to a white solid which was dried under vaccum at 50 °C to give 30 mg of the title compound. ^{1}H NMR ($CDCl_3$) 1.01–1.07 (m, 1H), 1.22–1.41 (m, 2H), 1.45 (s, 9H), 1.84–1.88 (m, 1H), 1.97–2.00 (m, 2H), 2.27–2.31 (m, 1H), 2.40–2.47 (m, 1H), 4.47 (m, v broad, 1H), 4.44 (m, v broad, 1H), 5.07 (s, v broad, NH). Calcd for $C_{12}H_{22}NO_4$ *m*/*z* 244.154883, found *m*/*z* 244.1541 and calcd for $C_{12}H_{21}NNaO_4$ 266.136828, found *m*/*z* 266.1362. $[\alpha]_D^{25} = -46.9$ (*c* 0.10099, MeOH), lit. $[\alpha]_D^{25} = -50.5$ (*c* 1, MeOH).

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